ANNALS OF SURGERY

VOL. 127 FEBRUARY, 1948 No. 2

THE SYNDROME OF THROMBOTIC OBLITERATION OF THE AORTIC BIFURCATION

RENÉ LERICHE* AND ANDRÉ MOREL

ROMANS, FRANCE

ONE OF US HAS DESCRIBED, in 1940,[6] a very peculiar and typical syndrome related to thrombotic obliteration of the end of the abdominal aorta. This new syndrome has no relation to the dramatic and well-known "saddle embolism" seen in cardiac patients and long since described in textbooks. The thrombotic disease appears to be a disease with a long course, presenting, for a long period, symptoms which have no meaning for the physician, unpleasant as they may be for the patient. It may remain compatible for years with a seemingly almost normal life. From the scarcity of reports in the world literature, it might be assumed to be rare. On the contrary, our feeling is, that its occurrence is not infrequent, and that adequate knowledge of its components will help to discover a fair number of cases which otherwise would remain misunderstood.

CLINICAL FEATURES

These appeared very clearly in our original cases (Leriche, 1940)[6], and they appear in all observations published since (Martorell, 1942, André Morel, 1943, Delannoy, Ameline, 1945, Moulonguet, 1945, Peycelon & Gallavardin, 1945, Frieh & André Morel, 1946, Servelle, 1946, Christophe, 1947 as well as in unpublished cases of our own).

As a rule, patients are young adults (the youngest of ours was 29); mostly males—but Delannoy reports a woman, aged 41.[3] In general, their past history is irrelevant. They come to the physician for one or the other of the following symptoms:

In the male: inability to keep a stable erection, the blood flow being insufficient to fill the spongious processes. (This sign is often met with in patients with high located arteritis of the ilio-femoral trunk, and is caused by vasospasm of the major pelvic arteries. It is not permanent, and sometimes disappears following bilateral lumbar sympathetic ganglionectomy, with favorable results). If the disease is left to itself, sexual impotency will soon be permanent.

* From the College de France, Paris.

Extreme liability to fatigue of both lower limbs. It is not the well-known "intermittent claudication," but an extreme weariness, which comes quickly on walking, sometimes even in ordinary standing position.

Usually a *global atrophy of both lower limbs* which it is difficult to appreciate as a normal limb lacks as a term of comparison. One must be on one's guard, not to overlook bilateral atrophy.

No trophic changes, either of the skin, or of the nails. Toes look normal. It is difficult to believe that the circulation is severely impaired. An important fact must however be noted: if there is an error in the diagnosis, and if an incision is made in the limb for peri-arterial sympathectomy (inadvisable in such cases), or any other operation, *the wound heals either very sluggishly or not al all.*

Pallor of the legs and feet, even when standing. At rest, the limb looks as if a Martin rubber bandage had just been released. When the legs are raised to the vertical, the pallor becomes striking, being like ivory or marble.

The *clinical investigation* reveals, moreover:

—that no pulse can be found, either in the leg, or in the groin. The iliac pulse is not felt. That of the aorta will be perceived very high-up, above the umbilicus.

—that oscillometric findings are: no oscillations in the leg or thigh; a slight thrill close to Poupart's ligament.

—that blood pressure is a trifle high in the upper limb; without any renal disturbance.

DIAGNOSIS

One should never diagnose a "neuritis" or a "polyneuritis" of the lower limbs, unless one has carefully examined the femoral pulses and the oscillometric curve. Bearing this in mind, diagnosis is easy. In fact, when a patient complains of impotency, or of severe fatigability of the lower limbs, or of pain in the thighs on exertion, if the physician finds alterations in the peripheral pulses, the provisional diagnosis of thrombotic obliteration of the aortic bifurcation may be made. When no pulse has been found on either side, in the dorsalis pedis, tibial, femoral and iliac arteries, when oscillometry at ankle, calf and thigh is confirmative, the diagnosis is probably accurate. Indeed, since our first description, the above-mentioned authors have discovered and diagnosed their cases with these simple means of investigation. The only difficulty is the recognition of an obliteration localized in both common iliac arteries, but, as thrombosis of the whole bifurcation often begins thus, inaccuracy of the diagnosis is of no consequence.

In almost all cases, clinical data, a shrewd study of the patient's history, and oscillometry, will lead to the discovery of the origin of all troubles. AORTOGRAPHY, as originally developed by Reynaldo Dos Santos,[4] will give a new and precise support to the diagnosis. It should be performed under short barbiturate anesthesia. If the patient is heavy, or presents signs of diminished

cardiac output, or has cyanotic legs with violaceous blurs, aortography is to be avoided, because in such instances its performance may lead to the extension of thrombosis, with fatal result. In properly selected cases, aortography gives a neat picture of the lesions, of their extent, of the thin net of anastomoses and by-ways which, through all subcutaneous, muscular, diaphragmatic, epigastric, ilio-lumbar, etc., arteries, allow a very scanty, though vital blood supply, to reach the ischemic limbs. Aortographies in man often show the same pictures as in Luigi Porta's hundred-year-old book (ligatures on animals, Milan, 1845).

PROGNOSIS

Aortic thrombosis, although apparently very well-borne for years (5 and even 10) always ends in gangrene. The onset of gangrene is not sudden, and not always bilateral. It is usually preceded by an increase in muscular atrophy of legs and thighs, and by a growing impairment of walking. Muscles vanish in a few weeks or months. There then appear edema, a general violaceous hue of the legs, with ecchymotic suffusions, and soon, sores on all pressure points, not only on the sacrum and back, but also on iliac crests, the rotula, the malleoli, the heel. Finally, gangrene supervenes, *i.e.*, dry gangrene, in the extremities, and in plates on leg, trochanter, and sides of the foot. Such an outlook of scattered and widespread dry gangrene, is typical enough. Lesions progress slowly accompanied by deep suffering which nothing can soothe, and death comes at length through heart, lung or kidney. The prolonged survival can be explained by the above-described anastomoses. The onset of the terminal period is due to upward and downward extension of the thrombosis, and sometimes to associated peripheric venous thromboses.

PATHOLOGY

The pathologic characteristics have been revealed in a small number of cases by postmortems, and mostly by the findings at operation. In some cases, the thrombosis seems to begin in one of the common iliac arteries. It then extends upwards, reaching the aorta and hampering the blood flow to the opposite side, but without, for a long time, stopping it totally. The final result is obliteration of both iliacs and aortic bifurcation.

In less frequent instances, the disease is at first on the aorta, and the iliac thrombosis is secondary. Whatever the beginning, thrombosis finally lies on at least 2 or 3 cm. of the aorta, and extends to both common iliac arteries, the obliteration of which is complete. Sometimes, the common iliacs have become hard, string-like sticks in which no lumen can be found. In some instances, the external wall of the artery is smooth and even, but there often exists, around the thrombosed aorta, an intensive peri-arteritis which attaches the vessel to prevertebral fibrous tissues, encircling the neighboring veins and lymphatic ganglia, and reaching the fourth sympathetic ganglion and the chain above. The aortic wall often bears atheromatous plates which will hinder the completion of the operative treatment. In such cases, the aortic lumen often con-

tains a big moulded, organized clot, which extends upwards in the aortic cavity, without adhesion to the intima in the portion of the vessel above the level of the thrombosis.

TREATMENT

One of us (Leriche) wrote, in 1923, that the ideal treatment of this condition, would be to resect the obliterated zone, and to bridge the vascular defect by graft. This could be accomplished if the thrombosis did not always strike the iliacs as well as the terminal aorta. In the present state of technic such an achievement seems impossible.

Nerve Supply Reduction. Efforts have been made to improve the peripheral circulation, through reduction of vaso-constrictor nerve supply to collateral ways and to trunks below the obliteration; and an attempt has been made to stop the fatal spread of thrombosis, *by removal of the thrombotic zone.* At the same time, vasoconstrictor impulses which originate in the aortic wall and result in vaso-spasm in the still free channels, ought to disappear. Such a procedure finds its justification in the experiments carried out by one of us with his co-worker Stricker in 1933 on dogs:[6] removal of the aortic bifurcation with its branches, with and without concomitant bilateral lumbar ganglionectomy: The latter condition produced gangrene, while the former yielded no severe troubles. With this objective in mind, we have performed bilateral ganglionectomies, and moreover resected the aorta and the obliterated iliacs.

Upper lumbar ganglionectomy. Up to 1946, we have practiced the upper lumbar ganglionectomy in 14 cases, the lower in five. Upper lumbar ganglionectomy was preferred. First, because it seemed desirable to meet as few collateral arteries, which should at all costs remain intact, as possible. By a lateral approach, just underlying the last rib, one usually reaches the sympathetic chain without destroying any vessel of notable size. Second, because, in view of nervous action, it seems advisable to operate as high up as possible, in order to enlarge the lumbar arteries as well as those of the lower limbs. The results proved satisfactory in the long run. The following case history is an example.

Case 1. (summarized) (Leriche). Melv. . . ., 35-year-old male, complains of troubles in walking, and sexual impotency (total) for 3 years. Claudicatio intermittens (100 meters). Examination on June 5, 1936: severe global atrophy of both lower limbs. When legs raised to the vertical, legs and feet turn ivory white. No pulse felt anywhere in the lower limbs nor in the iliac fossae, nor on the midline, except above the umbilicus, where it is felt very strongly. No oscillations (Boulitte's apparatus) in the lower third, upper third of the leg, nor in the thigh. Very small oscillations close to Poupart's ligament. No trophic changes except on nail of left big toe. Provisional diagnosis: Aortic obliteration.

June 13, 1936. *Operation.* Removal of first lumbar ganglion on the right side. Presence of an important number of large arteries in parietal muscles and in subperitoneal space. Owing to this, exposure of splanchnic nerve, which was originally planned, is given up.

Follow-up: Patient out of bed on 3rd day. Feels much better on operated side. Discharged on 10th day.

February 15, 1937. Demands to be treated for left side (same symptoms on left, as were formerly felt on right side: cramps, cold fingers, small ulcerations around nails).

February 16, 1937. *Operation.* Removal of 1st and 2d lumbar ganglia on left side. Same operative findings as on opposite side. Follow-up: Heals per primam.

In January, 1940: Feels well, does not suffer any longer in lower limbs, can walk longer. But afraid lest he should suffer same trouble in his hands (feels cramps, cold, numbness, moderate pain).

May, 1940: Very good condition; warm feet, good trophicity, walks well. Blood pressure 170/110 (this probably accounts for the symptoms in his hands).

Results are not always as good as in this case; nevertheless, one can say that patients always feel a functional improvement, and that some of them recover their sexual abilities.

The objection to upper lumbar ganglionectomy as the sole operation is that owing to this high approach, one cannot have a near vision of the aorta, nor confirm the diagnosis, nor decide on the possibilities of an aortic resection. We believe that aortectomy, whenever feasible, ought to be performed in order to check the spreading thrombosis, and to suppress arterio-arterial vaso-constrictor reflexes. A point to be noted is that when the pathologic aorta has not been removed, patients often continue to complain of pain in the back. This does not usually remain after aortic resection, and is probably due to peri-arteritis.

Having said that, we must acknowledge that the results of the bilateral lumbar ganglionectomy are good in the long run, if it is not performed too late. In addition to Case 1, two of our patients, after three years, lead a normal life, except that walking ability is reduced, though improving year after year. When this type of operation comes too late, there sometimes remains pain in a foot, intermittent pain which does not always hamper professional activities, but often compels the patient to take drugs at night. The man, who pre-operatively could no longer sleep, and spent his nights in an arm-chair, is then able to sleep in bed. He often remains liable to nightmares.

—*Terminal aortectomy with bilateral lumbar ganglionectomy.* The elaborate operation which consists in: terminal aortectomy, removal of one lumbar chain, section of the other, the whole being performed through one single incision, is sometimes practicable. We used it in the following case:

Case 2. (summarized) (Leriche) G. M. . . ., male, age 61, first seen in July, 1939, with the commencement of gangrene in right foot, and very severe bilateral pain. *Claudicatio intermittens* for several years. In 1936, noticed that right small toe became alternately white and blue; then, later on, painful at night; then, afflicted with a periungueal ulceration. A surgeon performed bilateral perifemoral sympathectomy, with subsequent suppression of all symptoms, except claudication. Improvement lasted for 2 years. In December, 1938, pain in both feet. His surgeon accomplished iterative periarterial sympathectomy—with subsequent aggravation: Left foot remained painful, cyanotic, with black spot on 4th toe. Exulceration of operative scar.

Examination on July 8, 1939: Patient in bad condition, tired, but no severe symptoms in viscera. B.P.: 180/100. Normal upper limbs. Lower limbs: Emaciated, cold, cyanotic in their lower part, mostly on left side. Torpid ulcer of operative scar on left

thigh. On the generally bluish color of left leg and foot, one can see four small gangrenous spots. On basal articulation of big toe, skin is necrotic, bordered by a torpid ulceration. All toes are violaceous; the 4th bears on its tip a spot of dry gangrene. Foot is icy cold, even under blankets. Skin is dry and squamous. Nails are thick and brittle. Neither pulse nor oscillations up to the groin. Both inner and outer sides of foot, show small veins which do not empty on pressure.

Left lower limb shows same alterations, though less advanced. Patient declares: no erection for 10 years; not the least sexual concern.

July 20, 1939. *Aortography* (under evipan anesthesia): Shows neat block of thorotrast shadow on edge of 3rd lumbar vertebra; from this point, there starts on left side a clearly-defined vessel which plunges into pelvis and gets lost there in numerous anastomoses. One of these anastomoses (originating on right side), seems to fill the left internal iliac artery, and, through it, perhaps the external iliac, as one can perfectly well see small branches which seem to belong to the hypogastric system, and inosculate with branches from internal aspect of thigh. The iliac circumflex is filled up on its whole course, and posteriorly, gets linked with two lumber arteries. On opposite side, the arterial network is less clear, more fragmentary, but of similar type. The diagnosis is clear; the case seems beyond the possibilities of a bilateral lumbar ganglionectomy; in order to try and soothe the pain and stop the extension of the disease, an attempt at aortectomy is decided upon.

Operation. July 24, 1939. Left iliac incision. Dissociation of external oblique muscle. Section of internal oblique and transverse muscles. Subperitoneal approach. Easy removal of left lumbar sympathetic trunk (from 2nd inclusive to 4th ganglion inclusive). Exposition and dissection of terminal aorta, which is surrounded by a *very dense periaortitis.* It is obliterated to a length of about 5 cm. Once it has been dissected, first from sclerous fat, then from the vena cava, it is ligated at about 1 cm. above the beginning of thrombosis. Crushing the artery with the ligature is very difficult, as one gets the impression that the arterial wall will not give way; then, abruptly, the wall collapses and the ligature is tied. The operator then follows the common iliac artery, carefully separating it from veins. The common iliac artery is obliterated, the external iliac too; a pulse is felt in the internal iliac. A ligature is tied just above the bifurcation of the common iliac artery. The removal of the common iliac (right) is then begun: Same findings as on opposite side. Use of same procedure: ligature above bifurcation of common iliac. From then on, the aortic bifurcation lies between three ligatures. Transection of left common iliac is troublesome, because of the presence of a hard calcified plate at this level. Section is performed just above, the aorta is also cut across, and the whole is retracted upwards and overturned to the right, in order to separate the right common iliac artery from the vein. Finally, section of right common iliac. All this has been done without the slightest bleeding. The right sympathetic chain is then looked for. It seems impossible to progress on the external aspect of the vena cava, owing to a large collateral which lies there. One passes under the vena cava, going from the midline to the external side of the column. Section of the chain. Local hemorrhage (stopped by muscle plug) prevents removal of 4th ganglion. Parietal closure without drainage.

Max. B. P.: Initial: 180; terminal: 170.

On removing patient from table: Both legs very warm; right foot: warm; left foot: warm, except on toes, which are cold.

Same findings on evening of operation; toes move.

On following day: Same condition, but patient slightly listless.

Right foot: Normal temperature and color; no pain.

Left foot: Cyanosis extends. Amputation is certainly necessary.

August 6, 1939. Amputation at upper third of thigh. Almost no bleeding from muscles. Artery and vein are thrombotic. Presence of many small vessels in posterior muscles.

Dissection of specimen: artery and vein, femoral and popliteal, are obliterated. Microscopic study (Pr. Gery, Strasbourg): "On the whole, arteries offer a picture of slow chronic endarteritis, the higher located, the more important and the more irregular. The muscular wall is affected with widespread sclerosis, mostly on big trunks. No mediaverkalkung. Larger veins: Recent thrombo-phlebitis (from 10- to 15-day old): It is less and less advanced as one progresses distally. Smaller veins: chronic vegetating endophlebitis in numerous points. Sciatic nerve: no changes, no sclerosis."

Follow-up: slow evolution of the amputation wound, as is the rule in such cases. No inflammatory reaction, no infection. At the end of August 1939, healing had hardly begun.

Owing to war, to the evacuation of the hospitals of Strasbourg, and to subsequent events, we do not know what has become of this patient. From our point of view, this does not alter the fact, that circulation in the right lower limb was considerably improved by aortectomy, with preservation of leg and foot on this side.

Such an aortectomy with bilateral sympathectomy, has been accomplished a number of times since this case. Cid Dos Santos in Lisbon had a patient who healed very easily, and, one year later, remained in excellent health. Delannoy operated upon a 41-year-old woman: in the first stage left lumbar ganglionectomy; in the second stage, transperitoneal aortectomy; very good result: three years later, she could do her shopping herself, and even occasionally "enjoy a short run."[3]

One of us used a slightly different technique in his first case:

Case 3. (summarized) (Morel[13]). Per. . . ., male, age 26, a truck driver. Past history: irrelevant. Very good health. First trouble two years ago: suffered from "cramps" in legs, on walking and running; was treated by family doctor, for "sciatica." Suffered very intensely in both legs, could not sleep for nearly three months.

Present condition: Running is impossible. Walking for a few hundred metres is stopped by very painful cramps. Feels cold in the legs, even in bed. Pain at night. For past few weeks: inability to reach a complete erection; coition hardly possible, ejaculation "unsatisfactory." Examination on February, the 12th, 1942: general condition seems good. Both feet are cold, toes are marble-white (patient states they are such at any time, and this is one of his major concerns). No abnormal perspiration. The anterior tibial, posterior tibial, popliteal and femoral pulses, not found, on either side. Subjective symptoms more severe on the left. In the upper extremities: the left radial pulse is better felt, and stronger, than the right. Oscillometry: no oscillations at all in the legs; very minute oscillations in both thighs. Blood pressure (left arm): 150/70. Normal heart. No neurologic symptoms.

Diagnosis: Juvenile arteritis thrombosans, with probability of obliteration of the aortic bifurcation.

February 16, 1942. Left lumbar sympathetic block—(nupercaïne)—: immediate warmth of foot, leg and thigh. Feeling of warmth present for two days. During these two days, can ride a bicycle with much rarer cramps. No sexual improvement.

February 20, 1942. Left lumbar block (nupercaïne): progressive warming-up of originally marble-white foot, which becomes red (1st and 2nd toes last of all). Feels better for one day.

February 23, 1942. Right lumbar block (nupercaïne): apparently no immediate action; 20 minutes later, foot becomes very warm, and remains normal for two days.

March 5, 1942. *Operation.* Spinal anesthesia (nupercaïne). Left iliac incision (subperitoneal approach). The sympathetic chain is very thin, but clearly recognizable. Resection on 4 cms. Dissection of the left common iliac artery, which looks abnormal, surrounded by a dense, reddish, adhesive cellulitis. No pulse seen nor felt. No blood

on puncture. The artery is very much like a big, solid rope-like structure. It is then resected (as high-up as possible towards the bifurcation). In the specimen: brown-red adherent clot, thick walls, yellowish, brittle inner layer). Parietal closure layer by layer.

Follow-up: Warm limb immediately following operation (objective and subjective warmth). Patient leaves Clinic on 13th day.

In the beginning: short walks; perfect result on operated side: no more cramps. Then, with longer walks, feels cramps again, but less severe than before operation. Above all, sexual condition much better. Coition possible.

May 2, 1942. Patient seen in consultation with Prof. Leriche. On this particular occasion (cold weather): left foot (operated side) is cold; right is *icy*. Pr. Leriche advises same procedure to be followed on opposite side.

May 4, 1942. *Operation* (Morel). Spinal anesthesia. Same approach as before, but on right side. Easier dissection than on left side (cellulous adhesions less dense and less troublesome). Right lumbar chain is resected on 5 cm. Then, the external iliac artery is found—a painstaking procedure, as it is a dry, rigid cord, about the size of a vas deferens. Distal section as low-down as possible, upwards dissection, liberation of bifurcation of the common iliac artery. The internal iliac seems to be thrombotic too, but, 2 or 3 seconds after it has been cut through, a severe bleeding occurs through its peripheral stump. Digital compression on pelvic margin for a few minutes, then quick seizure of stump with forceps, and ligature. Common iliac artery is then dissected about 3 cm., ligated as high as possible, and resected. Abdominal wall closed by layers.

Follow-up: Back home on 12th day.

August, 1942: Though all symptoms have not subsided, patient feels satisfied with present result. First of all, he can enjoy a very active life: does his job and drives a truck for most of the day; can walk about around his truck during loading and unloading. Circulation better or worse, following rest or fatigue, but, on the whole, he feels much better than before operations. Sleeps well, neither pain nor cramps in bed. On exertion, feels from time to time cramps in the calves, but they are milder and of much shorter duration than before. He states that sometimes, when walking is stopped because of a cramp, if he stops for a while, he is then able to resume his walk, with the feeling that he could go for miles without getting tired. Psychic condition much better. But the greatest improvement lies in the sexual abilities: the erection is readily obtained and kept; coition is normally accomplished, as it was before the onset of the disease. Potency but slightly diminished.

Examination: Both lower limbs are warm, feet are rosy. No abnormal sweating.

January, 1943: Patient gets married.

July, 1944: the couple has a child.

In January, 1946, patient states his good condition has undergone no change. Works very hard.

Pathology of specimen of left artery (Pr. J. F. Martin, Lyon): "Endarteritis thrombosans with no specific histologic findings."

This is a very safe procedure. The surgeon does not run the risk of a painstaking cleavage of a very adherent aorta, with subsequent severe shock. But, on the whole, when feasible, removal of the pathologic aorta is preferable. Such an operation was performed in the following case, with an excellent result:

Case 4. (summarized) (Frieh & André Morel)[5] Vou. . . ., 43-year-old male, a solicitor, is first seen on December 22, 1943, complaining of severe impairment of walking. Past history, irrelevant. Moderate drinking habit. Smokes heavily.

Since 1 year, claudicatio intermittens, which becomes more and more severe. (During winter preceding onset of disease, noticed that feet were usually cold though that winter was mild). At present, cannot walk more than 100 metres, without feeling a cramp.

Patient consults Dr. Gallavardin in Lyon, who diagnoses an arteritis of the lower limbs (April, 1943), and notes: "no pulses in dorsalis pedis and posterior tibial arteries; pulse hardly perceivable at the groin. Oscillometry: maximal oscillations: right ankle, 2 — left ankle: ¾ of a division—right thigh: 3 divisions; left thigh: 1½ division. Dr. Gallavardin notes on December, the 17th, 1943: "condition has become worse; no pulses felt in either lower limb."

Patient first examined by Dr. Frieh on December, the 22nd, 1943: no pulses at all in both lower limbs: aortic pulse, felt at the umbilicus.

Oscillometry: No oscillations at all. Both feet are white and cold. When put in dependent position, color is restored, but remains for several minutes even with feet raised above the horizontal. No pain, no trophic changes.

Sexual activity, reduced to nought. Diagnosis: probable obliteration of the aortic bifurcation.

January 7, 1944. *Operation.* Dr. Frieh, Dr. Morel. Local anesthesia (procaine). Iliac approach (left side). The left iliac artery is exposed subperitoneally: peritoneum is dissected up to the aortic bifurcation. Exposure and dissection of the vessels are difficult, owing to adherent lymphatic channels and small veins. The external iliac artery is ligated distally, and cut through; then its posterior aspect is freed, a maneuver which leads to the internal iliac (obliterated), which after dissection of 2 cm., is ligated and cut through. The common iliac artery is then freed upwards, the aortic bifurcation is exposed, and freed of posterior adhesions. Same procedure is applied to the right common iliac artery, which is ligated distally as far as possible, and cut. The aortic bifurcation does not "beat"; a ligature is drawn just above, and tied. A transverse section of the aorta is then performed just below the ligature (section through a very adherent clot). No bleeding at all. The last two ganglia of the left sympathetic trunk are removed; a drain is left in the vascular bed.

Follow-up: Uneventful recovery; foot warm on evening of operation; remains such on following days. On the 15th day, patient declares he has recovered his sexual abilities.

March, 1944: *Operation.* Ether anesthesia. Right lumbar ganglionectomy. Quick recovery.

September 28, 1945. Patient in very good condition; lower limbs are warm; claudicatio intermittens still exists; but cramps appear only after 300 meters. Good strength of lower limbs. Considerable exertion possible, provided it be of short duration. Patient has resumed all his professional activities. Sexual abilities: normal.

We have used a procedure of this type many times since (Leriche), and we are very satisfied with it.

Let us now try and see how the different types of operations should be used:

THERAPY — INDICATIONS

The scheme we are trying to outline is not meant to represent the ultimate truth. Our experience to date is of some value, as one of us happens to be among the men who have seen and treated the greatest number of patients afflicted with this too-little-known syndrome. No doubt our ideas will be subject to change, as they have already gradually changed since the first of our cases. But, at present, this is how we see the problem:

Indications should be outlined in particular according to anatomical and clinical data in every case. Schematically speaking, patients can be divided in three groups:

1. Good Cases. Patients who are still young, whose symptoms are essentially functional: fatigability of the lower limbs, disturbance of thermo-regulation thereof, genital troubles which are the more noticeable since they appear in full youth; obliteration of the bifurcation as demonstrated by clinical and oscillometric examination. Yet the tissue changes in the ischemic limbs, are still at their beginning: one could say they are liable to revert to the normal. At operation, the surgeon will find an easily cleavable aorta. The procedure will be completed without trouble on a good-risk patient.

Our opinion is that, in such instances, the surgeon should not hesitate. If everything seems suitable, after careful premedication, and, if judged advisable after a series of lumbar procaïne blocks, the *ideal* operation will be preferred—through left subperitoneal iliac approach, dissection of external, internal and common iliac arteries, freeing of the bifurcation, and removal, in one piece, of the whole aortic bifurcation and of its obliterated subsequent branches. Removal of the left lumbar sympathetic chain. Depending upon each case, but depending mostly upon the abdominal bulk and general condition of the subject, the operator will merely perform the section of the right lumbar chain, just above the pelvic margin; or, if the right lumbar chain is left intact in this first stage because of the difficulties of its approach, a few days later, the right lumbar ganglionectomy will be performed through a right, subperitoneal iliac approach.

Thus, the maximum chance of immediate and long term improvement will have been given the patient, in a very short time.

Such a procedure is usually very well tolerated. If gently and methodically carried out, under spinal anesthesia, which greatly helps to retract the abdominal muscles and gives a perfect relaxation, it will be followed by a simple and uneventful recovery in these cases, which—and we stress this point—are *good* cases.

2. Medium Cases. Patients are seen or diagnosed later in life: tired, thin subjects, whose circulation in the lower limbs is bordering on ischemia; patients aged over 40 and whose lower limbs begin to show trophic troubles, moderate but significant for the expert eye: meagre, marble-like feet, whose veins appear in hollow, small periungueal ulcerations, important callosities of the sole, striking atrophy of the muscles of the lower limbs. Blood urea rate is often a little above the normal, though the urinary output seems little affected.

In these cases, at operation the iliac arteries will be found to be embedded in a dense peri-aortitis, of which it will be very difficult to rid them. The bifurcation, above all, is stuck to the vertebral column, narrowly adherent to the vena cava. In these instances, considerable risk attends the complete freeing of the vessels and the removal of the thrombotic zone, *i.e.*: danger of a vascular tear causing hemorrhage which it is impossible to check in a deep

wound containing fragile tissues, which break under the forceps; or danger of severe post-operative shock, which sometimes causes death, whatever the treatment.

In these cases, we should advise the operation which, without severe risk, usually ensures a remarkable functional improvement: in a first stage, by a high-located incision (underlying the 12th rib, without resection of the rib, which is not necessary), removal of the 1st and 2nd right lumbar ganglia. A few days later, large left iliac approach (subperitoneal), and as extensive removal as possible, of the left lumbar chain (at least 3rd and 4th ganglia). At this moment, it will be easy to expose the vessels; perhaps the "ideal" aortectomy will be feasible, but if this entails a risk, it will be deliberately abandoned. If the dissection of the external and internal iliac arteries seems easy, they can be resected on the left side. But, again, if the least difficulty is encountered in these fragile patients, the surgeon will remember that the margin is narrow, between the successful operation, and a disastrous failure. Above all, one must insist on the important point: the action on the sympathetic innervation.

3. Poor Cases. Patients nearing 60, or adults seen in an advanced stage; patients emaciated through several months' suffering and insomnia; pale, listless at times. And especially patients who bear lesions of gangrene or pregangrene, such as those we described above. Such patients are dreadfully fragile. A careful medical preparation will be more than ever necessary, as well as a minute local treatment of the lower limbs in order to clean the ulcerations, to induce a subsidence of the lymphangitic processes, before any operation is attempted. At the time of operation, local anesthesia should be preferred, combined with a slow, atraumatic technic and a careful hemostasis. Following operation, rehydration, fulfillment of the metabolic needs of these subjects whose balance is always uncertain, are very necessary. And, sometimes, one will succeed in dragging back to life patients who seemed near their end.

What can be done with such patients? The great point is to divide the operative stages as much as possible: firstly, one should perform, on the side where the gangrene threatens most, a lumbar ganglionectomy through a high approach (in this way, one passes as far as possible from the dangerous zone and from the infected lymphatic ways); in a second stage, the opposite chain will be removed. If the condition of the patient improves sufficiently, it may be possible to use an iliac (low) incision and to perform at the same time the removal of the common iliac artery. Later on, this procedure will perhaps be feasible on the opposite side. Amputation of the definitive lesions of the extremities will thus be postponed as long as possible; the sympathetic and arterial operations will have improved the blood supply of the future amputation flaps; thus it will be possible to amputate at a lower site, than would have been practicable in the beginning. Healing will be infinitely better and quicker. When actual gangrene is present, amputation, preceded or followed by a lumbar sympathetic ganglionectomy, sometimes ensures a long survival.

A man, operated upon in 1932 (Leriche) (bilateral amputation at the thigh), still runs a garage, wheeling himself about in a special car. Another one, who underwent amputation on one side in 1939, had to be amputated on the other in 1947 (lumbar ganglionectomy had been unilateral).

On the whole, in instances so different, there should be no single way of proceeding, even if the general principles of therapy, as at present conceived, remain unaltered. These are: 1st, to improve the circulatory and trophic conditions, through distant sympathetic actions; and, secondly, to remove, whenever possible, the vascular lesions which are the origin of untimely pathologic reflexes.

Of the groups of patients which we have just endeavored to describe, one should remember that it is *time* which created them, time elapsed since the onset of symptoms, time lost in using minor therapeutic procedures or in overlooking the diagnosis. The syndrome is sufficiently clear-cut, to ensure an early accurate diagnosis, which allows an easy operation and an excellent cure. The study of all our cases leads us to the conclusion that, the earlier the necessary operation is performed, the better the results.

As regards the cases in which the pathologist discovers a thrombo-angiitic origin, we feel more and more inclined to advise the performance of an adrenalectomy in addition to the aforesaid therapeutic measures. Adrenalectomy slows down or stops the progress of the disease. It is, as a rule, followed by an improvement in the general condition of the patient, with subsidence of the erratic pain which often teases those who underwent a plain ganglionectomy.

Contraindications. In view of the choice of the operation, let us insist on some contraindications, which are very important, because of the fragility of such patients:

—During the operation, no ligature should be tried nor trusted, on easily-breakable aortas, of the "chicken's trachea-type": no safety can be expected from this sort of vessel, and it is better to leave the thrombotic part untouched, without attempting any resection.

—No attempt should be made to remove the pathologic zone when there exists too dense a peri-aortitis; attempts at dissection "at all costs" often give birth to severe shocks.

—No operation should be undertaken in *cases seen very late:* emaciated, dehydrated listless patients, who will not stand anything, and who are doomed to die, whatever the treatment.

TECHNICAL DATA

Incisions. When we say: *High* incision, we mean the type of incision we use for the surgery of the lumbar sympathetic ganglia, of the splanchnic nerve and of the adrenal (Leriche). The patient is disposed just as for an urologic lombotomy; the incision underlies the 12th rib and is parallel to it, cutting across the flank. The muscles are cut or dissociated (transverse); the

peritoneum is cleaved and retracted forward, and the lumbar chain is exposed in the bottom of the wound.

The *Low* incision is that described by one of us with his associate Fontaine (Presse Médicale, Paris, 1933, No. 92): curved incision, oblique inwards and downwards, nearing the iliac spine by two thumbs' breadth. Aponeurotic and muscular sections as in a MacBurney's incision, except that internal oblique and transverse are cut across after they have been carefully separated from the underlying fascia. The fascia will then readily be incised without opening the peritoneum, which is dissected from the internal iliac fossa, and retracted towards the midline.

For both these incisions, broad and curved retractors are necessary; we also advise the use, in addition to the scialytic light, of a portable projector, or spotlight, with parallel rays, which should be placed behind the operator's right shoulder, and which ensures a perfect vision of the deep planes.

Hemostasis of the Aortic Section. It seems best to insert, if possible in a normal zone above the thrombosis, or, if not, through the thrombotic zone, a sturdy braided silk ligature, which, for some time, will not slip. Under cover of this ligature, a continuous suture of the aortic section with a curved atraumatic "intestinal" needle (same as for the closure of a duodenal stump in gastrectomy) will be accomplished with fine silk; and then a second continuous suture hiding the first row, in order to suppress all chance of leakage. It is, of course, advisable to remove, after ligature and section of the aorta, the crushed clot which appears in its lumen and which would hamper the completion of the suturing process.

Hemostasis of the section of the iliacs. We insist upon the importance of always ligaturing a big vessel before its section, even if this vessel seems to be completely thrombotic and to no longer possess a lumen. In our Case 3, the distal end of the internal iliac was thus the origin of an hemorrhage which could have been fatal. We think that strong braided silk is the choice material for such a step.

SUMMARY

1. A new pathologic syndrome, first described in 1940 (Leriche) is depicted, and special emphasis put on its clinical features.

2. The evolution thereof is usually very severe, and operative measures should be preferred for its treatment.

3. Case reports illustrate the possible therapeutic measures.

4. Indications and contraindications in the treatment are discussed.

REFERENCES

[1] Ameline: A propos de la communication de M. Delannoy. Académie de Chirurgie, 1945, Paris, 71: 91.

[2] Christophe, Louis: Résection de l'aorte terminale et des deux iliaques primitives. Acta Chirurgica Belgica, Janvier, 56, 1947.

[3] Delannoy, Emile: Résection du carrefour aortique, et des bifurcations iliaques pour thrombose de l'aorte terminale. Guérison. (Rapport de M. Leriche). Académie de Chirurgie, 1945, 71, Février, Paris, 90–91.

[4] Dos Santos, R., Lamas & Caldas: Artériographie des membres et de l'aorte abdominale. Paris, Masson & Cie, éditeurs, 1931.

[5] Frieh, Ph. et A. Morel: Un cas d'oblitération du carrefour aortique (syndrôme de Leriche), traité par la résection du carrefour. Lyon Chirurgical, 1946, T. 41, No. 1, p. 17–18, 1946.

[6] Leriche, René: De la résection du carrefour aortico-iliaque avec double sympathectomie lombaire pour thrombose artéritique de l'aorte. Le syndrôme de l'oblitération termino-aortique par artérite. Presse Médicale, 1940, No. 54–55, 48, 601–604, 1940.

[7] Leriche, R. et P. Stricker: L'artériectomie dans les artérites oblitérantes. Etude expérimentale et thérapeutique. Masson et Cie, éditeurs, Paris, 1933.

[8] Leriche, R.: Physiologie pathologique et Chirurgie des artères. Principes et méthodes. (de la Chaire de Médecine du Collège de France). Masson et Cie, éditeurs, Paris, 1943.

[9] Leriche, R.: Thromboses artérielles. Physiologie pathologique et traitement chirurgical. (de la Chaire de Médecine du Collège de France). Masson et Cie, éditeurs, Paris, 1946.

[10] Martorell, F.: El sindrome de obliteracion termino-aortica por arteritis. Revista clinica espanola. April 5, No. 2,130, 1942.

[11] Martorell, F. and J. Valls Serra: Trombosis cronica obliterante aortico-iliaca. Medicina Clinica. April T. 2, No. 4, P. 304–315, 1944.

[12] Martorell, F.: Accidentes vasculares de los miembros. Salvat, editores, Barcelona-Buenos Aires, 1945.

[13] Morel, André: Thrombose de la terminaison de l'aorte avec syndrôme de Leriche. Artériectomie, sympathectomie lombaire. Presse Médicale, Mars, No. 11, p. 137–138, 1943.

[14] Moulonguet, P.: Résection de la bifurcation aortique pour troubles ischémiques. Résultat au bout de 18 mois. Paris, Académie de Chirurgie, 21 Mars, 1945, 71: 137–138.

[15] Peycelon and Gallavardin: Lyon Chirurgical, 40 Novembre, 1945, 778–781.

[16] Servelle, M.: Résection du carrefour aortique et des iliaques primitives pour thrombose artéritique. Résultat de 15 mois. (Rapport de M. Bergeret). Paris, Académie de Chirurgie, 1946, **32**: 3–4, **72**: 224–225.

1, Rue de l'Écosserie
Romans, France

THE PROBLEM OF MAINTAINING THE CONTINUITY OF THE ARTERY IN THE SURGERY OF ANEURYSMS AND ARTERIOVENOUS FISTULAE

NOTES ON THE DEVELOPMENT AND CLINICAL APPLICATION OF METHODS OF ARTERIAL SUTURE*

HARRIS B. SHUMACKER, JR., M.D.
NEW HAVEN, CONN.

FROM THE VASCULAR CENTER, THE MAYO GENERAL HOSPITAL, GALSEBURG, ILL., THE SURGICAL HUNTERIAN LABORATORY, THE JOHNS HOPKINS UNIVERSITY, BALTIMORE, MD., AND THE DEPARTMENT OF SURGERY, THE YALE UNIVERSITY SCHOOL OF MEDICINE, NEW HAVEN, CONN. AIDED IN PART BY A GRANT FROM THE OFFICE OF NAVAL RESEARCH, THE UNITED STATES NAVY.

IT has long been recognized that the ideal method of treating aneurysms and arteriovenous fistulae involving important arteries is the extirpation of the lesion combined with some procedure which permits maintenance or reëstablishment of the continuity of the affected artery. Although steady progress has been made experimentally in methods of suturing arteries, especially during the past half century, and although these methods have occasionally been used in patients, until recent years it has been the general feeling that such procedures were fraught with too great danger to make their use advisable in the surgery of aneurysms and fistulas in man.

The lateral closure of a wound of an artery by ligation antedates the experimental approach to the problem of vascular suture.[1] Nevertheless, the principles which underly vascular repair, the precautions which must be observed, the hazards which are entailed, and the methods which are applicable were first established by experimental investigations. A number of authors, notably Watts,[2] Guthrie,[3] Horsley,[4] and Matas,[5] have reviewed these contributions. In their papers one can find reference to those who have played an important part in this development—Asman, Gluck, v. Horoch, Jassinowsky, Burci, Heidenhain, Murphy, Silberberg, Napalkow, Dörfler, Salvia, Clermont, Dorrance, Abbe, Jaboulay and Briau, Payr, Bougle, Salinari and Virdia, Thomaselli, Salomoni, Jensen, Amberg, Hubbard, De Gaetano, Reinsholm, Garré, Exner, Höpfner, Carrel, Guthrie, and others. Interest in the problem of experimental vascular repair has not waned and in recent years numerous papers have appeared describing these efforts. Among the recent contributions the demonstration by Murray[6] that anticoagulants are helpful in preventing thrombosis is particularly noteworthy. Of all those interested in vascular surgery, the name of Carrel[7] will always be held in especial esteem for, though excellent work had been done previously, his beautifully performed experiments, and those of his associates, did more than anything else to revive and maintain interest in the use of these methods.

Without minimizing the prime importance of these experimental studies, one is glad to give due credit to those who first applied the technics of arterial

* Presented before the Society of Clinical Surgery, Baltimore, Md., November 1, 1946.

suture in man. In 1759, Hallowell, following the suggestion of Lambert,[1] closed a small wound of the brachial artery by placing a pin through its margins, elevating the lacerated area, and tying a ligature about it. According to Höpfner,[8] and to Matas,[5] the first successful lateral arteriorrhaphy in man after Hallowell's case was performed by Postempski, in 1886, when this surgeon succeeded in closing the rent in the femoral artery which he had accidentally made in draining an abscess. Reports of other successful instances of lateral suture followed, and, by 1903, Höpfner was able to collect 30 reported cases.[8]

The first end-to-end suture of an artery in man was reported in 1897 by Murphy,[9] who, in a traumatic arteriovenous fistula, closed the small wound of the vein, resected the damaged portion of the artery, and accomplished a successful end-to-end anastomosis by invaginating the proximal into the distal segment. Two additional successful operations utilizing Murphy's method were reported the same year by Pascha.[10] Thus, the first end-to-end sutures of arteries in man were done by means of the invagination technic of Murphy. Subsequently it became apparent that direct approximation of the divided ends of the artery was a superior method.

Not many years after the demonstration of Carrel, and his associates, that arterial defects could be successfully bridged by means of a vein transplant, this method was applied in a patient. In 1906, Goyanes[11] treated a luetic popliteal aneurysm by proximal and distal ligation and reëstablished blood flow by anastomosing the femoral artery to the distal end of the divided femoral vein and the proximal end of the divided popliteal vein to the distal segment of the popliteal artery. Good circulation through the venous segment and into the popliteal artery was observed. The foot maintained good circulation and a feeble dorsal pedal and posterior tibial pulse persisted during the six-day period of observation. In 1907, Lexer[12] reported the case of a man with a traumatic axillary aneurysm resulting from the unfortunate efforts of a surgeon to reduce a dislocation of the shoulder, in which he excised the aneurysm and sutured a segment of saphenous vein into the arterial defect. The patient died of delirium tremens on the 5th postoperative day. Autopsy demonstrated the patency of the vein graft and of the brachial artery. Lexer subsequently used this procedure in a few other cases. In 1916, Bernheim reported the first successful case in the American literature.[13] He used a vein graft to bridge a defect in the popliteal artery following excision of a luetic aneurysm.

In discussing Bernheim's paper, Halsted agreed that this was the ideal method of treatment and felt that the indications for it had been clear-cut in this case and the result excellent. He referred, however, to a case in which six years previously he had asked Bernheim to carry out a vein transplantation after he had unavoidably sacrificed a segment of the popliteal artery in the course of excision of a sarcoma. In this instance thrombosis in the vein segment had occurred. He stated: "The most serious objection to the 'ideal' or vein-grafting operation is perhaps this: that in case of failure the thrombosis

which starts in the graft may extend either centrally or peripherally, or in both directions, from the interpolated vein into the artery and, thus, involve important anastomotic branches which would not have been threatened with occlusion if the artery had been merely ligated, or the sac merely excised or plicated. The transplanted vein is, consequently, a menace, for in at least two-thirds of the cases in which the 'ideal operation' has been practiced, thrombosis has occurred in the insert." To be sure, the hazard of thrombosis appeared to be greater after vein transplantation than after end-to-end suture or lateral arteriorrhaphy. Nevertheless, these remarks of Halsted, one of the most courageous of surgeons, and one who was vitally interested in experimental and clinical problems of vascular surgery, probably typify the skepticism which has existed as to the justifiability of such measures. Consequently, although the total number of clinical cases in which some type of reparative procedure has been performed has risen to a considerable figure, the method has been applied with relative infrequency.

I believe that it will be worth while to review my personal experiences with reparative measures in aneurysms and arteriovenous fistulae, because they confirm the general usefulness and reliability of these methods, emphasize certain difficulties in their application and certain causes of failure, and particularly because they demonstrate that the resolution of the surgeon to preserve the continuity of the artery whenever possible is the chief factor which determines the frequency with which such procedures will be carried out.

CLINICAL MATERIAL AND RESULTS

My experience with surgical treatment of aneurysms and arteriovenous fistulae includes about 300 cases. In a few aneurysms of the aorta or origin of the innominate artery, wiring and coagulation proved the only feasible method. In one innominate aneurysm and in 290 other lesions of peripheral arteries the more classical surgical means of extirpation were utilized. This report deals specifically with 34 cases in which some type of reparative procedure was accomplished. It does not include a number of other cases in which such procedures were considered and started but were abandoned because of various circumstances.

CRITERIA FOR SELECTION OF CASES

The criteria for the selection of suitable cases can be divided into two periods. In the beginning it was my practice to exclude all cases except those in which I could be relatively certain that normal arterial structures could be utilized and in which it appeared likely that the procedure could be accomplished without undue difficulty. If only the cases are considered in which the lesion involved those arteries upon which the main blood supply to a part is dependent and in which repair is most desirable—the innominate, common and extracranial portion of the internal carotid, subclavian, axillary, brachial, iliac, common femoral, femoral, and popliteal—I find that I performed only four reparative procedures in 138 such cases (2.9 per cent). I then deter-

mined to carry out a repair in every instance in which this could possibly be performed without sacrificing collateral arteries and without leaving *in situ* obviously badly damaged portions of arteries. This altered approach resulted in the repair of arteries in 30 of the last 57 cases (52.6 per cent). Included were a small number of cases in which the outcome of the procedure appeared questionable to me at the time of operation because of the degree of local damage or the presence of infection; as will be pointed out later, this group includes practically all of the failures. Repair was undertaken in these instances in the hope that some might be successful and in an effort to test the limits of applicability of such methods. I did not fear difficulty from extension of any thrombus which might occur because of the excellence of the collateral circulation.

Although I believe that the attitude of the surgeon is of paramount importance in the application of reparative procedures to the surgery of aneurysms and fistulae, the anatomic situation which one finds at operation often precludes such measures. In the first place, there may be thrombosis of the distal artery. This occurrence has made impossible any arterial repair in a number of my cases. I presume that very extensive arterial obliterative disease will sometimes make such procedures impossible. Since most of my cases have been traumatic in nature, this factor has not been important. In one case of rather extensive medionecrosis of the popliteal artery a successful vein graft was performed. In traumatic lesions extensive damage to the artery is often a determining factor in preventing the restoration of continuity, at least by the simpler means such as lateral arteriorrhaphy or end-to-end anastomosis. In contrast to the limited injury to the artery which is the rule when aneurysms or fistulae have resulted from stab wounds, for example, there is generally extensive injury when these lesions have resulted from shell fragments, land mines, or bullets, as was the case in almost all of my patients. There is frequently gross and much more often microscopic injury to the artery, not only in the immediate neighborhood of the aneurysm or fistula but some distance from it. Whether the damage which is evident only on microscopic examination is a real threat to successful arterial repair, only further experience will tell. In the cases of arteriovenous fistula the simpler means of repair, such as ligation or transfixion of the fistula, lateral suture, or end-to-end anastomosis, often cannot be applied because of the extent of local trauma. In my experience the majority of the arteriovenous communications were not simple fistulae but were associated with one or several saccular aneurysms as well. Sometimes these saccular aneurysms arose from the veins or from the fistula itself, but many of them originated in the artery. Obviously, in the latter cases a segment of artery must be excised and, unless the ends can be so mobilized that they can be approximated, the only means of restoring continuity is by a vein transplant.

A very common finding which has made it seem unwise to perform an end-to-end suture or a vein graft, has been the presence of some important collateral artery so near the end of the undamaged portion of the vessel that

it would have had to be sacrificed in order to make such a repair possible. Except for the rare cases where the local situation makes it evident that continuity of the artery can be safely maintained by some simpler procedure, such as ligation or transfixion of a fistula, it seems clear that definitive surgery should not be attempted unless there is good evidence that the collateral circulation is satisfactory. Knowing that the collateral circulation was apparently adequate and that it depended in part upon these collateral vessels to which I

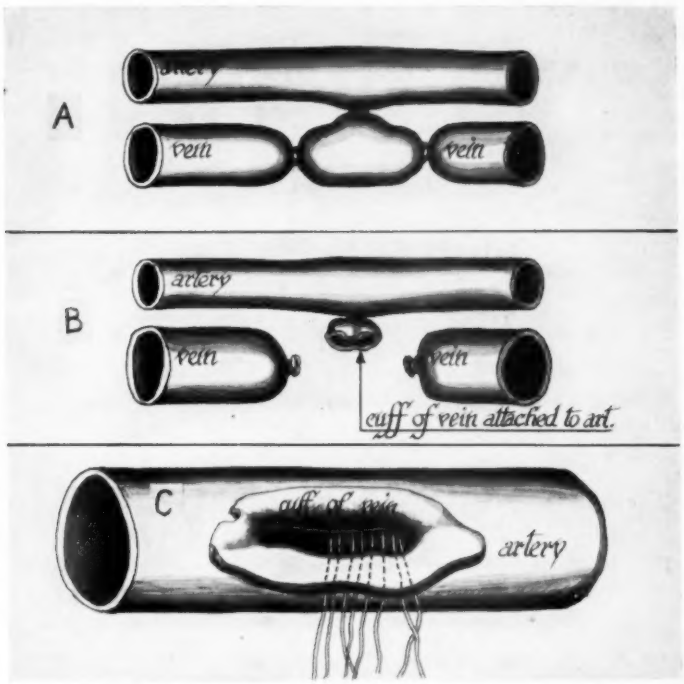


FIG 1.—Methods of Repair of Arterial Defect in Arteriovenous Fistula:

(A) The fistula has been ligated with silk at its origin from the artery. A transfixing ligature is next placed.

(B) The vein has been divided above and below the fistula and the ends transfixed. The cuff of vein will now be plicated so as to reinforce the ligated fistula.

(C) Method of lateral suture. A cuff of vein is left attached. The suture is accomplished with interrupted mattress sutures.

have referred, I have felt it unwise to sacrifice any of them. I did not reëxamine the collateral circulation with these collateral arteries temporarily occluded, a procedure which I feel, in retrospect, might have made repair of the artery justifiable in a number of cases in which it was not attempted. I have not felt that associated nerve lesions requiring suture were a contraindication to arterial repair. In these cases the nerves have been dissected free, the aneurysm or fistula has been excised completely or subtotally, and the arterial

repair accomplished. Following this procedure the necessary nerve suture has been performed.

METHODS OF REPAIR

In the present series of cases four types of repair have been carried out—ligation or transfixion of the fistula, lateral arteriorrhaphy, end-to-end suture, and vein transplantation. In one instance an arteriovenous fistula was simply ligated and transfixed. In others the fistula was ligated, transfixed, and buttressed with a segment of the divided vein (Fig. 1, A and B). In cases of lateral suture the freshened edges of the rent have been stripped of adventitia and approximated with interrupted mattress sutures (Fig. 2). In performing

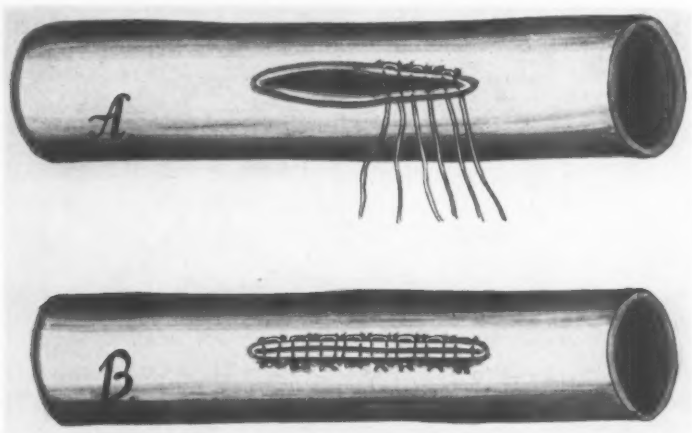


FIG. 2.—Method of Lateral Arteriorrhaphy: The edges of the defect are approximated with everting mattress sutures.

lateral suture in cases of arteriovenous fistulae a cuff of vein has been left (Fig. 1, C) and this has been used to reinforce the closure. In end-to-end sutures four evenly spaced mattress sutures have been placed and have been used as traction sutures for the placing of other everting mattress sutures in order to complete the anastomosis (Fig. 3). A similar technic was used in vein grafts (Fig. 4). The segment of vein was reversed so that the proximal end of the vein was sutured to the distal end of the artery and *vice versa*, thus guarding against difficulty with any valves which might be present in the insert. In all types of repair the adventitia was carefully stripped off and the vessels were washed out with saline and kept moist with liquid petrolatum or saline solution. Rubber-shod serrafine artery clamps were used for temporary occlusion of the vessels. Fine straight or curved artery needles were employed. Since silk sutures were not available, No. 120 cotton sutures were used. This suture material is about as fine as No. 5 zero silk. When vein grafts were used the venous segment was excised from an accessible vein of suitable caliber. In cases of arteriovenous fistula in which a ligation of the fistula was not performed, the affected segment of artery and vein, together with the fistula, was

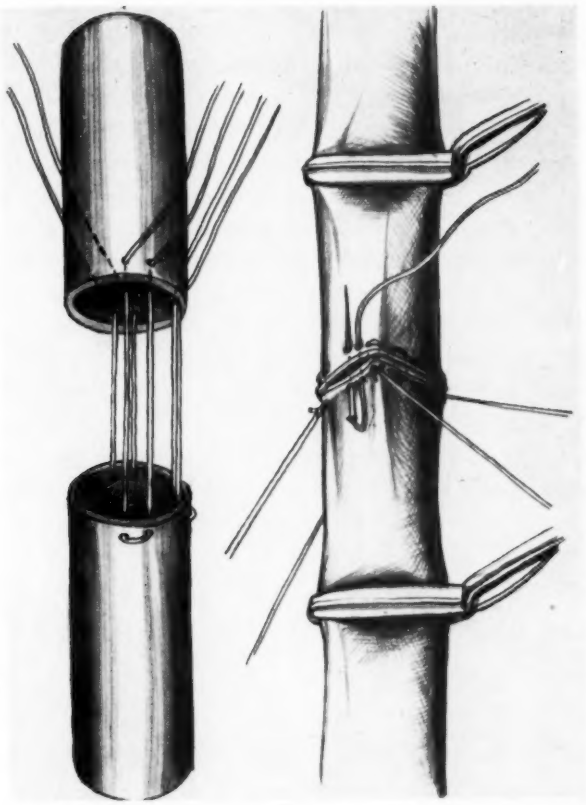


FIG. 3.—End-to-end Suture: Four mattress sutures are placed through the ends of the vessels at equidistant parts. Traction upon these converts the cylindrical ends of the vessels into a square, with the intima everted. Closure is completed with additional interrupted mattress sutures.

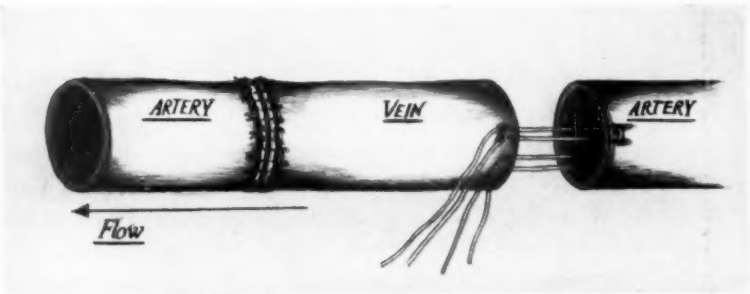


FIG. 4.—Vein Transplantation: The vein has been sutured with interrupted mattress sutures to the distal end of the artery. Suture to the proximal end of the artery has been started.

excised. Some of the arterial aneurysms were completely excised. In some, the sac was opened after dissection and temporary occlusion of the artery proximal and distal to the aneurysm, following which the sac was completely or subtotally resected. All involved peripheral nerves were freed and identified before excision of the sac wall.

Anticoagulants were used in most cases of lateral suture, end-to-end suture, and vein graft. Except in those instances in which an adequate prothrombin

TABLE I.—*Cases of Arteriovenous Fistula Treated by Ligation and Transfixion of the Fistula*

Case No.	Age of Patient	Duration of Lesion in Mos.	Location of Lesion	Pre-operative Sympathectomy	Estimated Diameter of Fistula in Mm.	Anticoagulant Therapy	Period of Postoperative Follow-up in Mos.	Result
1	36	9	Carotid at bifurcation	0	3	0	1.5	Excellent
2	31	4	Common carotid	0	10	0	1	Excellent
3	22	4.5	Common carotid	0	5	0	1	Excellent
4	26	9	Popliteal, middle 3rd	+	7	0	4	Excellent except for slight ankle edema
5	35	9	Popliteal, middle 3rd	+	5	0	1	Excellent
6	19	6	Popliteal, distal 3rd	+	6	+	2	Excellent except for slight ankle edema
7	45	10	Popliteal, middle 3rd	+	5	0	1	Excellent
8	20	9	Femoral, middle 3rd	+	5	+	1	Excellent
9	27	11	Femoral, proximal 3rd	+	8	0	1	Excellent
10	25	6	Femoral, proximal 3rd	0	4	+	1	Excellent
11	32	7	Femoral, proximal 3rd	+	5	0	1	Excellent
12	23	7	Femoral, proximal 3rd	+	3	0	1.5	Excellent
13	21	4.5	Axillary, distal 3rd	0	3	0	1	Fistula recurred in 2 days. Excised 2 weeks later, with good result

level had been obtained by preoperative administration of dicumarol, 50 mg. of heparin was given intravenously as soon as the decision to attempt repair was made, and was continued at intervals of four hours until a suitable response had been obtained from dicumarol. In the majority of cases dicumarol was continued for three weeks. Often a small amount of fibrin foam was placed in the wound. This seems to help in hemostasis and does not jeopardize the vascular suture. The use of anticoagulants is discussed in detail in another paper.[14]

In some cases, sympathectomy had been performed before operation in an effort to increase the efficiency of the collateral circulation.[15]

RESULTS

The essential data are summarized in Tables I to IV. In these tables the cases have been segregated according to the method of repair employed. In Table I are listed 13 cases in which the fistula was ligated and transfixed and the continuity of the artery maintained. In Case 13 a simple ligation and transfixion was performed; in all the others the fistula was ligated and transfixed at the point of its emergence from the artery and was buttressed by a segment of the divided vein. The ages of the patients ranged from 19 to 45 years. The duration of the fistula at the time of surgery ranged from 4 to 11 months. The fistula was between the carotid artery and the jugular vein in three instances, between the popliteal vessels in four, the femoral in five, and the axillary in one. In eight cases sympathectomy had been performed because of poor collateral circulation. Anticoagulants were used in three cases. In Case 6 heparin was given at the time of operation and until a satisfactory prothrombin level had been obtained from the administration of dicumarol. In the other two cases dicumarol had been given preoperatively for several days. In all three, dicumarol was continued for from two to three weeks. In a fourth case (Case 13) a single dose of heparin was given at the time of operation.

The size of the fistula varied, the diameter ranging from 3 to 10 mm. I was surprised to find that even large fistulae could be ligated close to their origin from the artery without causing any demonstrable narrowing or distortion of the artery. In six cases saccular aneurysms were present. These sacs arose from the vein in three cases, from the fistula in two, and from the artery in one. In the latter case the sac had a small neck which could be ligated and transfixed. Case 10 was complicated by a fracture of the femur and Cases 4 and 6 by peripheral nerve injuries requiring suture. In the one, neurorrhaphy was done at the time of operation; in the other it was deferred until a later date.

In Case 13 in which simple transfixion of the fistula was performed, recurrence of the bruit and thrill was evident two days after operation. The fistula was excised with quadruple ligation two weeks later, with good result. The result was excellent in all the other cases. There was no evidence of recurrence or of dilatation of the artery. The two limbs were of equal warmth and color except in those instances in which sympathectomy had been performed; in these patients the affected foot was warmer than the other. All the pulses distal to the site of anastomosis were present and full, and were judged by all observers to be about equal to those in the contralateral extremity. The results of oscillometry were approximately the same in the two extremities except for two of the cases in which the limb had been sympathectomized, where oscillations were slightly greater upon the operated side. There were no abnormal physical findings except in two cases in which there was slight edema of the ankle which became progressively less with the passage of time.

In Table II are listed data on five cases in which an arterial defect was repaired by lateral suture. The patients were all in their twenties; their

vascular lesions were of from 2.5 to 6.5 months' duration at the time of operation. Two were instances of traumatic arterial aneurysm, three of arteriovenous fistula. The brachial artery was affected in one case, the subclavian in two, and the femoral in two. In none of the patients had sympathectomy been performed. The arterial defects were from 3 to 12 mm. in length. The artery appeared in good condition in three cases, fair in one, and rather poor in one. There was only slight constriction of the artery following

TABLE II.—*Cases in Which Artery Was Repaired by Lateral Arteriorrhaphy*

Case No.	Age of Patient	Duration of Lesion in Mos.	Type of Lesion	Location of Lesion	Lgth. of Arterial Defect in Mm.	Condition of Artery	Degree of Constriction	Anti-Coagulant Therapy	Period of Follow-up in Mos.	Result
1	27	2.5	Saccular aneurysm*	Brachial, distal 3rd	4–5	Good	Very slight	+	2	Excellent until hemorrhage on 13th P. O. day. Reexploration. Excision and ligation with good results
2	25	3.6	Saccular aneurysm	Subclavian, distal 3rd	3	Good	Very slight	+	2.5	Excellent. Hematoma evacuated on 10th postoperative day
3	20	6	A-V	Subclavian, distal 3rd	12	Good	Very slight	0	1.7	Excellent
4	27	6	A-V	Femoral, proximal 3rd	12	Fair	Slight	0	1.7	Excellent
5	29	6.5	A-V	Femoral, middle 3rd	12	Poor	One-half diameter	0	1	Poor. No pulse felt distally after operation. Reexploration in 3 hrs. Segment thrombosed Excised with good result

* Grossly infected. Had ruptured subcutaneously.

repair in all cases except one; in this case the diameter of the artery was reduced by 50 per cent. Heparin was given for two days in Case 1; in Case 2 it was given until the prothrombin level had been rendered satisfactory; in this case dicumarol was continued for 11 days.

In Case 1 the artery was bathed in a pool of pus. Continuity of blood flow through the artery was maintained, but on the 13th postoperative day a hemorrhage occurred through the sutured defect. On reëxploration there was no evidence that healing had taken place at the line of suture. The segment was excised and the artery ligated, with good result. In Case 5 the extent of damage to the artery and the narrowing of its lumen after closure of the defect were so extensive as to make me wonder at the time whether the segment should not be excised. Shortly after operation it was evident that thrombosis

had occurred. The thrombosed segment was excised, with good result. There had been no propagation of thrombus either centrally or peripherally. This patient did not receive anticoagulant therapy.

In the other three cases an excellent result was obtained. The color, warmth and pulses in the two extremities were the same. The results of oscillometry were equal in the two limbs in one case and moderately reduced on the operated side in one; in the third oscillometric studies were not made.

TABLE III.—*Cases in Which Artery Was Repaired by End-to-End Suture*

Case No.	Age of Patient	Duration of Lesion in Mos.	Type of Lesion	Location of Lesion	Preoperative Symp.	Lgth. of Artery Excised in Mm.	Period of Follow-up in Mos.	Result
1	20	5.7	Saccular aneurysm	Brachial, distal 3rd	0	1.5	2	Excellent
2	35	7.5	Saccular aneurysm	Brachial, distal 3rd	0	1.5–2	2	Excellent
3	27	8	Saccular aneurysm	Brachial, proximal 3rd	0	1.5–2	3.5	Excellent
4	28	8.5	Saccular aneurysm	Brachial, middle 3rd	0	1.5	2	Excellent
5	23	5.5	Saccular aneurysm	Axillary, distal 3rd	+	2–2.5	2	Excellent
6	19	6	Saccular aneurysm	Brachial, middle 3rd	0	1.5	2	Excellent
7	24	6	Saccular aneurysm	Brachial, distal 3rd	0	2	1	Segment thrombosed Good circulation
8	21	3	Saccular aneurysm	Brachial, distal 3rd	0	2	5	Probably thrombosed and recannulized
9	29	3	A-V and saccular aneurysm	Axillary, distal 3rd	0	2	4	Excellent
10	29	3	A-V	Femoral and profunda arteries. Femoral vein	0	3-femoral 2-profunda*	2.5	Excellent

* Anastomosis between proximal end of profunda and distal segment of femoral artery.

In Table III are listed data upon ten cases in which the artery was repaired by an end-to-end suture. The patients ranged in age from 19 to 35 years. The lesions varied in duration from 3 to 8.5 months. Eight of the patients had an arterial saccular aneurysm, two had an arteriovenous fistula. In one of these there was a saccular aneurysm in addition to the fistula. The lesion involved the brachial artery in seven cases, the axillary in two, and in one a double fistula was present between the femoral and the profunda femoral arteries and the femoral vein. In one patient sympathectomy had been performed before operation.

It was necessary to excise segments of artery ranging from 1.5 to 3 cm. in length. In lesions of the axillary and brachial vessels length of artery was gained by adducting the arm to the body and flexing the forearm upon the arm. After completion of the operation, position of the extremity was maintained by the use of elastic bandages or by means of plaster splints. In one

case in which the fistula involved both the femoral artery and the profunda, the divided ends of the femoral artery could not be approximated. It was, however, possible to approximate without tension the proximal end of the profunda to the distal stump of the femoral artery (Fig. 5). In five patients there were injuries of peripheral nerves which required lysis, and in two of them neurorrhaphy was necessary.

The patients were followed for a period of from 1 to 5 months. In eight of the patients there was every evidence to substantiate the patency of the artery. In one case (Case 7) trauma to the brachial artery had resulted in an aneurysm near its distal end. The sac lay partly in the belly and tendon of the biceps muscle. After its excision it was feasible to suture together the divided ends of the artery. The artery was small and its distal segment was somewhat scarred. Further resection of the distal end, in order to have available for suture more normal artery, was impossible because the vessel

TABLE IV.—*Cases in Which Continuity of Artery Was Restored by Vein Transplant*

Case No.	Age of Patient	Duration of Lesion in Mos.	Type of Lesion	Location of Lesion	Pre-op. Sympathectomy	Lgth. of Vein Graft in Cm.	Source of Vein Graft	Period of Follow-up in Mos.	Result
1	26	4.2	A-V and saccular aneurysm	Femoral, distal 3rd	0	2	Saphenous	3	Excellent
2	19	5	A-V	Femoral, middle 3rd	0	2	Branch of femoral	3	Excellent
3	26	4	A-V	Femoral, distal 3rd	+	5	Saphenous	3	Excellent
4	35	?	Saccular aneurysm	Popliteal, middle 3rd	+	2	Small saphenous	4	Excellent
5	36	6 yrs.	Saccular aneurysm	Femoral, proximal 3rd	0	2.5	Femoral	1.5	Excellent
6	24	5.3	Saccular aneurysm	Brachial, middle 3rd	0	2.5	Saphenous	1.2	Thrombosis. Good circulation maintained.

bifurcated nearby. This patient received heparin at the time of operation and was started on dicumarol shortly afterwards. By mistake he was given very large doses of dicumarol during the afternoon and night; though no signs of bleeding appeared the anticoagulants were discontinued and vitamin K was administered. Evidence of thrombosis of the sutured segment was soon noted, though the hand maintained good circulation. In another patient (Case 8) the anatomic condition seen at operation was similar to that in the preceding case; indeed, the damage to the distal artery was more extensive. Although the patient continued to have a good radial pulse, the ulnar pulsation and oscillometric readings were significantly reduced. Some observers felt that the anastomosis had remained patent, but it was my belief that thrombosis had occurred and had, perhaps, been followed by recannulization.

In Table IV data are given concerning six patients in whom an arterial defect was repaired by vein transplantation. The patients ranged in age from 19 to 36 years. Their vascular lesions were traumatic in origin in five cases; in one a saccular popliteal aneurysm had resulted from medionecrosis of the artery. The traumatic lesions were from four months to six years in duration. Three were instances of arterial aneurysm, three of arteriovenous fistula. In one case there was a saccular aneurysm in addition to a fistula. The brachial artery was involved in one patient, the popliteal in one, and the femoral in four. Sympathectomy had been performed in two cases. The vessel for grafting was taken from the main saphenous vein in three patients, from the small saphenous in one, from the femoral in one, and from a branch of the femoral in one. One patient had a fracture of the femur, and in another neurolysis and neurorrhaphy were necessary. All the patients were given anticoagulants.

FIG. 5.—Arteriogram of Case 10, Table III: A fistula between the femoral and profunda femoral arteries and the femoral vein has been resected with end-to-end suture of the profunda artery proximally to the femoral artery distally. Arteriogram taken ten weeks later by injection of 70 per cent diodrast into the common femoral artery reveals excellent filling of the femoral artery. No narrowing is noted at the suture line.

The patients were followed for a period of from five weeks to four months. The patency of the vessels was demonstrated by various studies in five cases; in the sixth thrombosis occurred but good circulation was maintained. No explanation is evident for the failure except that the suture may have been technically imperfect because of the small size of the artery. I have not seen such a small brachial artery in any other case. Arteriograms taken of several patients demonstrated patent vessels and showed no postoperative dilatation of the venous insert. In those cases in which the vein had been larger than the artery, the arteriograms demonstrated the relative diameters of the vein transplant and the artery to be much the same as they were observed to be at operation (Fig. 6). In those cases in which the artery and vein were observed to be approximately the same size at operation, arteriograms taken later showed their relative diameter to be unchanged (Fig. 7).

It was evident that reparative procedures had been successful in 28 of the 34 cases. In one case (Case 13, Table I) a fistula recurred, and in one case of lateral suture in the presence of gross infection (Case 1, Table II) healing did not follow. In one case of lateral suture (Case 5, Table II), in one case of end-to-end suture (Case 7, Table III), and in one case of vein transplantation (Case 6, Table IV) thrombosis of the repaired segment oc-

curred. In one case (Case 8, Table III) several observers had some doubt as to the outcome. I felt that thrombosis and subsequent recannulization had taken place.

In analyzing these failures, I feel, in retrospect, that the first patient should have been treated differently—instead of a simple double transfixion of the fistula, the vein should have been divided and used to reinforce the transfixed fistula, as was done in other cases. There is much to suggest that

FIG. 6

FIG. 7

FIG. 6.—Arteriogram of Case 2, Table IV: An arteriovenous fistula between the femoral artery and vein has been resected, with transplantation of a segment of a large branch of the femoral vein, about 2 cm. in length, in order to bridge the arterial defect. Arteriogram taken seven weeks after operation reveals the vein insert and the artery to have relative diameters about equal to those observed at completion of operation.

FIG. 7.—Arteriogram of Case 1, Table IV: An arteriovenous fistula and saccular aneurysm involving the femoral vessels has been resected and a segment of saphenous vein, 2 cm. in length, introduced as an insert in the arterial defect. There was no dilatation of the venous segment at completion of the anastomosis and none is noted on arteriogram taken ten weeks later.

ligation of vessels in continuity is, in general, unwise and that division of ligated vessels is preferable. The one exception in which I feel that simple multiple transfixion gives excellent results is in the case of patent ductus arteriosus in which the technic of Blalock has proved a simple and generally reliable method.[16] In this situation, in contrast to others, the anatomic factors perhaps favor success of the procedure. The ductus is actually not as long as

it appears to be when stretched out by dissection, and once ligation is accomplished the pulmonary artery and the aorta naturally fall back into close proximity, thus, eliminating stretching and tension of the ligated fistula. In regard to the second case in which the aneurysm was grossly infected, I know of no alternative procedure which would have made successful healing of the artery more likely. In three cases I feel that the local damage to the artery was sufficiently extensive to account for the thrombosis which ensued. The lateral suture in Case 5 in Table II should probably not have been carried out —instead the damaged segment should have been excised and repair accomplished by end-to-end suture or vein graft. In addition, anticoagulants should have been used. In the other two cases further resection of the injured distal segment of artery appeared to be prohibited by the proximity of the point of bifurcation to the severed distal end of the vessel. In the remaining case (Case 6, Table IV) I know of nothing that could have been done to ensure success. The vessel was unusually small and it is possible that the repair was not technically perfect, although at the time of operation it appeared to be satisfactory and a free flow of blood through the vein insert was present at time of closure.

In addition to the complications in the cases just discussed there were a few others. One patient had a postoperative hematoma which required exploration of the wound two hours after the original operation (Case 2, Table IV). The vein graft was found to be functioning well and the bleeding to be coming from a small branch to a muscle. This was clamped and ligated. Three other patients had hematomas of the wound (Case 2, Table II, Cases 2 and 4, Table IV). All were being given anticoagulants. In one the hematoma was aspirated; in two the wound was reëxplored, and in both there was evidence that diffuse capillary bleeding had occurred. Anticoagulants were stopped, and no further difficulty was encountered. Two patients (Cases 4 and 5, Table IV) had a mild wound infection which did not interfere with the success of the vascular repair.

In evaluating the patency of the repaired artery various examinations were utilized. The presence of a warm, well-colored foot was obviously not sufficient evidence upon which to judge the repair to be successful, nor was the presence of distal pulsations. The presence of a radial pulse after brachial or axillary repair or of a dorsal pedal pulse after a femoral or popliteal repair is of little significance, for such pulses may be present after ligation of main arteries proximally, provided the collateral circulation is adequate. The presence of *all* pulses distal to the site of repair, equal in volume to those of the contralateral limb, is felt to provide evidence of successful maintenance of continuity of the artery. For example, when full popliteal, posterior tibial and dorsal pulses are present after repair of the femoral artery, the patency of this vessel is apparent. In addition, criteria of success included visible patency by arteriograms in those cases in which such studies were made, and oscillometric results comparable to those in cases in which the patency of the artery was

established by arteriographic examination and in excess of those observed in proved cases of arterial ligation.

The oscillometric studies are recorded in Table V. Data are available upon 24 cases in which the artery remained patent, and upon five cases in which thrombosis occurred or in which ligation had to be performed because of recurrence of the fistula or because of hemorrhage. The three cases of carotid fistula are excluded, and data are not available in one case of peripheral fistula in which the repair was successful, and in one case in which thrombosis occurred. In each case only oscillometric measurements distal to the site of

TABLE V.—*Oscillometric Studies After Arterial Repair*

			Oscillometry at Ankle or Wrist		Oscillometry at Calf or Forearm		Oscillometry at Thigh or Arm	
Type of Repair	Artery Repaired	No. of Cases	Reading Average	Per Cent of Reading in Contralateral Limb	Reading Average	Per Cent of Reading in Contralateral Limb	Reading Average	Per Cent of Reading in Contralateral Limb
Ligation of fistula	Femoral	5	2.3	96	5.1	96	3.5	95
	Popliteal	4	5.1	75	7.6	95	...	..
Lateral arteriorrhaphy	Subclavian	2	2.5	83	3.8	70	4.5	88
End-to-end Suture	Axillary	2	1.0	37	1.5	41	2.2	44
	Brachial	4	2.5	83	2.8	51	...	..
	Femoral	1	3.0	60	4.5	50	7	100
Vein transplantation	Femoral	4	3.1	67	4	50	4	67
	Popliteal	1	2.0	67	3	43	...	..
Successful repairs	Total	24	2.9	79	4.3	68	4.0	68
Unsuccessful repairs	Total	5	1.0	17	0.9	16	0.5	18

repair are included in the figures presented. It will be seen that the results of oscillometry were good in those cases in which the continuity of blood flow through the repaired artery was maintained and poor in those in which the segment was occluded by thrombosis or was ligated. The figures for the ankle or wrist, the calf or forearm, and the thigh or arm are 2.9, 4.3 and 4.0 in the first group, and 1.0, 0.9 and 0.5 in the second. The percentage of the values in the normal contralateral limb is 79, 68 and 68 in the first group, and 17, 16 and 18 in the second.

Of considerable interest is the observation that, in general, oscillations were about equal in the operated and normal extremities in those cases in which a fistula was simply ligated and transfixed, were only slightly reduced

in the cases of lateral arteriorrhaphy, and were reduced to a somewhat greater degree in the cases in which end-to-end suture or vein graft was performed. This observation came as a surprise since in all of these cases comparison of the color, warmth and pulsations in the operated and normal limb revealed no noticeable difference. It does not appear that this reduction in oscillations is explicable on a basis of local or general vasoconstriction since the limbs showed no evidence of vasospasm. Furthermore, in some cases in which sympathectomy had been performed a similar reduction in oscillations was noted. Arteriograms showed no evidence of constriction at the site of repair. Nevertheless, it was felt that diminished expansibility of the suture line might serve as a possible explanation and it was realized that a functional stenosis at systole might be masked in arteriograms by the movement of the artery with pulsations during the exposure of film.

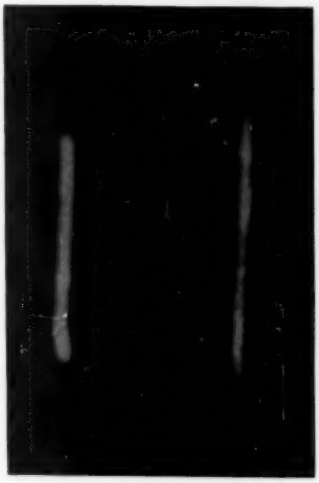


FIG. 8.—Arteriograms of carotid arteries of dogs which have been divided and repaired by end-to-end suture six weeks previously. The segments have been ligated and suspended on a frame so that each was of the same length as *in situ*, and have been injected with iodide solution at mean systolic pressure. No constriction of the lumen at site of suture is seen.

In order to investigate this hypothesis, end-to-end anastomoses of the carotid arteries of dogs were performed. Six weeks later a segment of the artery, including the suture line, was excised after measuring mean systolic pressure in the artery. Two points of the vessel wall were marked and the intervening distance measured *in situ*. The artery was ligated proximally and distally, injected with iodide solution at mean systolic pressure, and suspended on a frame so that the segment was of the same length as it had been in the animal, and roentgenograms were taken (Fig. 8). No constriction was visible; indeed, it was difficult, or impossible, to identify the line of anastomosis. Too few experiments have been performed to demonstrate that such results are uniform; nevertheless they suggest that functional stenosis is not the explanation of the reduction in oscillations. To be sure, the diminished oscillations are of little practical concern since there was little or no evidence of any functional circulatory impairment.

In general, the results of arterial repair were excellent. Except for some edema in two of the patients listed in Table I, a symptom which diminished progressively with the passage of time, the circulatory status appeared normal. None of the patients had sensitivity to cold of the hand or foot—a fairly common sequela in cases in which an aneurysm or fistula was treated by a procedure involving ligation of the artery.[15, 17] Excluding a few patients in whom exercise-tolerance could not be judged fairly because of motor paralysis or fracture, and a few patients who had fatigability of the extremity before oper-

ation, and at a time when blood flow through the affected artery was intact, none of the patients had any appreciable decrease in tolerance of exercise. In contrast, those patients in whom surgical treatment had necessitated ligation of a major artery as a rule had fatigability. For example, those with ligated popliteal or femoral arteries could walk only an average of about seven-tenths of a mile before onset of extreme fatigue or cramps in the calf.[15]

Discussion.—The ideal method for the surgical treatment of aneurysms and arteriovenous fistulae is extirpation of the lesion and maintenance or restoration of the continuity of the artery. In this regard it is fitting to pay tribute to Lambert who, in 1759, long before arteries had been repaired in man or in experimental animals, conceived the idea of preserving the involved artery. At his suggestion, as I mentioned previously, Hallowell accomplished closure of the small rent in an artery by twisting a thread about a pin placed through the lips of the wound. In a letter to Hunter, which was read on June 15, 1761,[18] Lambert stated after discussion of a patient who was left with some functional impairment following treatment of an aneurysm by proximal and distal ligation: "This case, in particular, made me turn my mind to the operation for the aneurysm, and made me wish to see it done with some alteration in the method, so as to make less disturbance in the circulation of the part. I recollected all that I had seen or read of the effects of styptics, of pressure, and of ligatures in the case of hemorrhage. I considered the coats and motions of arteries, and compared their wounds with the wounds of veins, and other parts. I reflected upon the process of nature in the cure of wounds in general, and considered, in particular, how the union of divided parts was brought about in the operation of harelip, and in horses' necks that are bled by farriers. Upon the whole, I was in hopes that a suture of the wound in the artery might be successful; and if so, it would certainly be preferable to tying up the trunk of the vessel." Unfortunately, his brilliant reasoning was to wait long for additional application while surgeons struggled with the technical difficulties of curing aneurysms and fistulae without undue risk of life and while the fundamental principles of vascular suture were being developed.

Such reparative procedures can be carried out in a large number of cases. Though local anatomic factors sometimes preclude the use of these methods, the attitude of the operator determines, perhaps more than anything else, the frequency with which these procedures will be applied. A high degree of success can be anticipated; nevertheless, up to the present time one cannot assume that the results of arterial repair will be uniformly successful.

Since this is the case, it is advisable to do everything possible to make certain that the collateral circulation is adequate before definitive surgery of the aneurysm or fistula is attempted. An exception can be made in the rare case with poor collateral circulation in which the local findings at operation make it evident that the continuity of the artery can be maintained by some very simple means, such as transfixion of a fistula. Even though arterial repair is planned and accomplished, the same care should be exercised to

preserve all collateral arteries as is essential when methods are used which necessitate ligation of the affected artery. If a collateral vessel requires division in order to complete repair, the collateral circulation should be rechecked and its adequacy established with this vessel temporarily occluded. I feel that employment of this principle would have increased the number of reparative operations in the present series of cases.

The chief hazards of surgical repair of arteries are hemorrhage, thrombosis, and subsequent development of aneurysmal dilatation at the site of repair. The chief local factors which endanger the success of the repair appear to be damage to the wall of the artery, infection, and such small caliber of the lumen as to make accurate approximation difficult. Most important of all, in the success of the operation, is careful observance of the well-established principles of surgical repair of vessels.

In the present series of cases postoperative hemorrhage occurred only once, in a case in which the sutured artery lay in a pool of pus and in which healing did not take place. Some of the early, and recent, investigators have demonstrated that successful repair can be accomplished in the presence of infection. Nevertheless, from the earliest experiments it has been recognized and repeatedly demonstrated that the danger of hemorrhage and of thrombosis is increased by infection.

In my experience thrombosis has occurred in only three cases of lateral arteriorrhaphy or end-to-end suture in which the local arterial damage was sufficiently extensive to raise doubts in my mind at the time of operation that the artery would remain patent, and in one vein transplant to an exceedingly small brachial artery. In retrospect, I feel that a wider excision and vein grafting would have been a preferable procedure in the former cases and would have been applicable in at least one of them. As mentioned previously, thrombosis in the last case may have resulted from imperfect technic due to the small size of the vessel, although the completed anastomosis appeared at the time of operation to have been properly performed. In the introduction to this paper I quoted some remarks of Halsted on the danger of extension of the thrombus so as to compromise important collateral arteries. I believe that clinical and experimental data suggest that such propagation of a thrombus is unlikely provided the collateral circulation is adequate, for extension of a thrombus is not apt to occur if the circulation proximal and distal to the site of repair is kept active by collateral blood flow. Furthermore, the chance of thrombosis occurring, or of its propagation if it should occur, can be lessened considerably by the use of anticoagulants. In the reported series there was nothing to suggest extension of the thrombus in those cases in which thrombosis did take place. In the one case in which the occluded segment was excised the thrombus was sharply limited to the immediate area of the repair.

There was recurrence of an arteriovenous fistula in one case in which the fistula was simply transfixed and ligated in continuity, a procedure which appears to be unwise. As far as I know, up to the present time no aneurysms have developed at the site of repair. Should this unfortunate event take place,

it appears likely that it would occur within the first few weeks or months after operation, as it did in Holman's case,[19] and not years later when atherosclerotic changes might add an additional hazard to its extirpation. Under such circumstances it would seem that the original procedure could still be looked upon as justifiable; such patients should be able to withstand surgical cure of the aneurysm with no more risk than would have been entailed had the artery been ligated at the original operation.

In any vascular repair certain principles must be followed. The artery must be handled gently to avoid local injury, its intima must be kept moistened with saline solution or mineral oil, the artery must be occluded only by some nontraumatizing means such as rubber-shod artery clamps, and the adventitia must not be allowed to fall into the suture line. The edges of the vessel must be carefully brought together with fine suture material in such a way as to approximate intima-to-intima. Strict asepsis must be maintained. These principles gradually became apparent in the course of the early experiments. Most of them are evident from the early work of Jassinowsky,[20] Murphy,[9] and Dörfler,[21] and they were exemplified in the experiments of Carrel and Guthrie.[22] Some disagreement existed as to the choice of suture material, but it has long been established that only the finest nonabsorbable sutures should be used. Silk has been almost universally used, but the present study demonstrates that also very fine cotton sutures are satisfactory.

In order to facilitate the accurate approximation of the inverted intima, Carrel suggested the use of three initial tension sutures placed at equidistant points.[23] Horsley[4] suggested the use of a metal bar for holding the three traction sutures. In the cases I have reported, four interrupted mattress traction sutures have been used, because it was found easier to space four sutures at equal distance from one another than three. The use of four traction sutures was a contribution of Frouin.[24]

Practically every type of suture has been recommended. Jassinowsky[20] used interrupted sutures, Burci[25] a continuous suture. Both tried to avoid inclusion of the intima, as Crafoord[26] still does in his cases of coarctation of the aorta. Others, however, have largely abandoned the idea; since the work of Silberberg,[27] Napalkow[28] and Dörfler,[21] most workers have included the intima in the suture. Jaboulay and Briau[29] introduced the use of interrupted everting mattress sutures. Clermont,[30] working with veins and Dorrance[31] with arteries, used a continuous mattress suture. Horsley[4] recommended a continuous cobbler's stitch. In the present series of operations I have used interrupted mattress sutures. Although I have found both continuous and interrupted, plain and mattress sutures to be satisfactory in experimental animals,* I have felt that the everting mattress sutures gave one greater assurance

* Since completion of this paper a statistical study of the complications following end-to-end suture of arteries in dogs suggests that everting mattress suture technics are superior to those in which the ends of the vessels are approximately layer-to-layer with plain sutures.

(H. B. Shumacker, Jr. and R. I. Lowenberg. Experimental Studies in Vascular Repair. 1. Comparison of Reliability of Various Methods of End-to-End Arterial Suture. Surgery. In Press.)

of accurate intimal approximation without interposition of adventitia and that such anastomoses could be accomplished without noticeable constriction. In repair of peripheral arteries the vessels can be easily and securely closed with interrupted sutures; in certain situations, however, continuous sutures are preferable. For example, the continuous mattress suture, which Blalock[32] has recommended for subclavian-pulmonary anastomosis in congenital heart disease where there is impaired pulmonary blood flow, is the suture of choice since it gives one the best opportunity to secure a tight closure and, since once the anastomosis is completed, the posterior portion of the suture line is relatively inaccessible for any further repair which would be necessary should a leak be present.

Up to this point I have not mentioned the use of mechanical aids in the repair of arteries. The use of permanent nonabsorbable intraluminal prostheses, such as the glass rods of Abbe,[33] is doomed to failure from thrombosis. The removable glass splint of De Gaetano[34] is obviously better. The soluble rod technic recently presented by Smith[35] can undoubtedly be used with success, but I have felt no need for intraluminal splinting and have preferred the more classical methods of repair. A number of external aids have been introduced in order to permit sutureless anastomoses. The absorbable magnesium ring technic of Payr[36] had extensive experimental and some clinical trial and has some merit, as have the modified rings of Lespinasee, Fisher and Eisenstaedt.[37] Recent attention has been directed to nonsuture methods by the ingenious vitallium tubes which Blakemore, Lord and Stefko[38] have used successfully. I have preferred suture technics because of several considerations. The sutured vessel has no permanent rigid, nonabsorbable, partially constricting ring around it as does the vessel repaired by the vitallium tube method. I believe in the hands of those experienced in vascular suture, the suture method carries less risk of subsequent hemorrhage and no significantly increased hazard of thrombosis. Though I have had little experience with the nonsuture method, I have attempted to use it in a number of cases but have abandoned it in each case because of certain difficulties. In some I had trouble in finding a vein of suitable size; in others I could not use the tubes because their length would have necessitated occlusion of collateral vessels near the end of the severed artery. In one case in which I completed a vein graft by this method, a brisk hemorrhage occurred as the wound was being closed, which was due to slipping of the tube out of the proximal artery even though it had been tightly ligated in place with several silk ligatures. Undoubtedly, this brief personal experience is not representative of that of workers who have devoted more attention to this technic. It is my feeling, however, that those who are confronted with problems of vascular repair can more profitably devote their energies to obtaining proficiency in vascular suture rather than in nonsuture methods. Perhaps the nonsuture method has its greatest sphere of usefulness in the hands of the untrained vascular operator who, on rare occasions, may encounter a case requiring anastomosis of blood vessels.

The question of establishing the patency of the artery after vascular repair

deserves some comment. From the earliest reports to the most recent, one finds that there has been a tendency to judge the results of repair of arteries to be successful on extremely uncertain grounds. Some observers have used the absence of gangrene or other ischemic damage as evidence of success. Regardless of the incidence of gangrene in cases in which a given artery is ligated, the absence of such a disaster does not prove in any case that the repair has been followed by persistent patency of the repaired segment. Others have cited good warmth and color and a palpable dorsal pedal or radial pulse as evidence of success, observations which may follow the ligating of main stem arteries if the collateral circulation is adequate. If by success we mean preservation of the lumen of the repaired vessel, we must be careful to obtain good evidence of its patency, a matter which has been discussed previously.

One also finds in the literature numerous statements to the effect that if a vascular repair remains patent for only a short time, it may be useful in tiding the patient over a precarious period until the collateral circulation becomes well-established. Should thrombosis occur gradually over a period of time, with slow narrowing of the lumen, one might expect this occurrence to favor development of collateral circulation, just as a partial proximal ligation seems to exercise such an influence. Actually, I know of no work to suggest that such thromboses bring about slow gradual occlusion of arteries; on the contrary, when thrombosis occurs it seems generally to be rapid and complete. One can imagine that in a badly traumatized limb some of the collateral channels might be functioning poorly because of compression from hemorrhage into fascial compartments and by attendant vasospasm. In such a circumstance, if a repaired artery could be kept open for a few days it might serve a useful protective purpose. In most circumstances, and certainly in the surgery of aneurysms and fistulae, one can look upon an arterial repair followed by thrombosis as having served no useful purpose. It has, indeed, subjected the patient to certain additional hazards, hazards which, however, as I have previously pointed out, are minimal and of little practical concern provided the collateral circulation is adequate, no collateral vessels have been destroyed, and anticoagulants are used.

Altogether there seems every justification for performing reparative or restorative procedures instead of arterial ligation whenever such methods can be applied. The recent report of Freeman[39] is in agreement in this regard. Brooks[40] has stressed the advisability of arterial repair in cases of arteriovenous fistula during a period when many of his contemporaries have recommended other measures. It is fair to say that the results of successful repair in cases of aneurysm or fistula are superior to any method which necessitates sacrificing the continuity of the affected artery.

SUMMARY

1. Thirty-four cases in which the continuity of the affected artery in cases of aneurysms or arteriovenous fistulae was maintained or restored by some method of vascular repair are reported.

2. The methods of repair, the choice of cases for application of such methods, and the results in successful and unsuccessful cases are discussed.

3. The historical development of the principles of vascular repair and of their clinical application is reviewed briefly.

REFERENCES

1 Lambert: Medical Observations and Injuries. Vol. II, London, 1762. Cited by Watts.[2]

2 Watts, S. H.: The Suture of Blood Vessels: Implantation and Transplantation of Vessels and Organs. An Historical and Experimental Study. Bull. Johns Hopkins Hosp., **18**: 153–179, 1907.

3 Guthrie, C. C.: Blood-Vessel Surgery and Its Applications. New York, Longmans, Green & Co., 1912.

4 Horsley, J. S.: Surgery of the Blood Vessels. St. Louis, C. V. Mosby & Co., 1915.

5 Matas, R.: Surgery of the Vascular System in Keen's Surgery. Vol. 5, pp. 1–130. Philadelphia, W. B. Saunders Co., 1920.

6 Murray, G.: Heparin in Surgical Treatment of Blood Vessels. Arch. Surg., **40**: 307–325, 1940.

7 Carrel, A.: The Surgery of Blood Vessels, *etc.* Bull. Johns Hopkins Hosp., **18**: 18–28, 1907.

8 Höpfner, E.: Über Gefässnaht, Gefässtransplantationen und Replantation von Amputirten Extremitäten. Arch. f. Klin. Chir., **70**: 417–471, 1903.

9 Murphy, J. B.: Resection of Arteries and Veins Injured in Continuity: End-to-end Suture: Experimental and Clinical Research. Med. Record, **51** 73–88, 1897.

10 Pascha, D.: Über die Arteriennaht. Cited by Watts.[2]

11 Goyanes, J.: Neuvos trabajos de Chirurgia vascular; substitucion plastica de las arterias por las venas, o arterioplastia venosa, aplicada, como neuvo metodo, al tratamiento de los aneurismas. El siglo med., **53**: 561–564, 1906.

12 Lever, E.: Die Ideale Operation des arteriellen und des arteriellvenösen Aneurysma. Arch. f. Klin. Chir., **83**: 458–477, 1907.

13 Bernheim, B. B.: The Ideal Operation for Aneurysms of the Extremity: Report of a Case. Bull. Johns Hopkins Hosp., **27**: 93–95, 1916.

14 Shumacker, H. B., Jr., D. I. Abramson and H. H. Lampert: The Use of Anticoagulants in the Surgery of Aneurysms and Arteriovenous Fistulas: With Particular Reference to Dicumarol. Surgery, **22**: 910–918, 1947.

15 Shumacker, H. B., Jr.: Sympathectomy as an Adjuvant in the Surgery of Aneurysms and Arteriovenous Fistulas. I. Sympathectomy Performed Before or at Time of Operation. Surgery, **22**: 571–596, 1947.

16 Blalock, A.: Operative Closure of the Patent Ductus Arteriosus. Surg., Gynec. and Obst., **82**: 113–114, 1946.

17 Shumacker, H. B., Jr.: Sympathectomy as an Adjuvant in the Surgery of Aneurysms and Arteriovenous Fistulas: II. Sympathectomy Performed after Operation. Surgery, **22**: 597–610, 1947.

18 Lambert: Cited by E. A. Smith. Suture of Arteries: An Experimental Research. Oxford University Press, London, 1909.

19 Holman, E.: Arteriovenous Aneurysms. Macmillan Company, New York, 1937.

20 Jassinowsky, A.: Die Arteriennaht: Eine Experimentalle Studie. Inaug. Diss. Dorpat, 1889.

21 Dörfler, J.: Über Arteriennaht. Beitr. z. Klin. Chir., **25**: 781–825, 1899.

22 Carrel, A., and C. C. Guthrie: Uniterminal and Biterminal Venous Transplantations. Surg., Gynec. and Obst., **11**: 266–286, 1906.

23 Carrel, A.: La technique operatoire des anatomoses vasculaires et la transplantation des viscerès. Lyon Méd., **98**: 859–864, 1902.

[24] Frouin, A.: Sur la suture des vaisseaux. Presse Méd., **30**: 233–34, 1908.
[25] Burci, E.: Recherche sperimentale sul processo di reparazione delle ferite long. delle arterie. Abstracted in Centralbl. f. Chir., **17**: 897–898, 1890.
[26] Crafoord, C.: Personal communication.
[27] Silberberg, O.: Über die Naht der Blutgefässe. Klinische und experimentalle Untersuchungen. Inaug. Diss., Breslau, 1899.
[28] Napalkow: Naht von Herz und Blutgefässen. Diss. Moskow, 1900. Abstracted in Ztschr. f. Chir., **27**: 596–597, 1900.
[29] Jaboulay, M., and E. Briau: Recherches expérimentales sur la suture et la greffe artérielles. Lyon Med., **81**: 97–99, 1896.
[30] Clermont, G.: Suture latérale et circulaire des veines. Presse Méd., **1**: 229–233, 1901.
[31] Dorrence, J. M.: An Experimental Study of Suture of Arteries: With a Description of a New Suture. ANNALS OF SURGERY, **44**: 409–424, 1906.
[32] Blalock, A.: Physiology and Surgical Treatment of Congenital Cardiovascular Defects. Bull. New York Acad. Med., **22**: 57–80, 1946.
[33] Abbe, R.: The Surgery of the Hand. N. Y. Med. J., **59**: 33–40, 1894.
[34] De Gaetano: Cited by Guthrie, N. Y. Med. J., 1894.
[35] Smith, S.: The Soluble Rod as an Aid to Vascular Anastomosis. Arch. Surg., **41**: 1004–1007, 1940.
[36] Payr, E.: Beiträge zur Technik der Blutgefässe und Nervennaht Nebst Mittheilungen über die Venvendung eines resorbirbaren Metalles in des Chirurgie. Arch. f. Klin. Chir., **62**: 67–93, 1900.
[37] Lespinasse, V. D., G. C. Fisher and J. Eisenstaedt: A Practical Mechanical Method of End-to-end Anastomosis of Blood Vessels. J. A. M. A., **55**: 1785–1799, 1910.
[38] Blakemore, A. H., J. W. Lord and P. L. Stefko: The Severed Primary Artery in the War Wounded. A Nonsuture Method of Bridging Arterial Defects. Surgery, **12**: 488–508, 1942.
[39] Freeman, N. E.: Arterial Repair in the Treatment of Aneurysms and Arteriovenous Fistulas: A Report of Eighteen Successful Restorations. ANNALS OF SURGERY, **124**: 888–919, 1946.
[40] Brooks, B.: The Treatment of Traumatic Arteriovenous Fistulas. Southern M. J., **23**: 100–106, 1930.

789 Howard Ave.
New Haven, Conn.

CONSERVATIVE SURGERY IN TUMORS OF BONE* WITH SPECIAL REFERENCE TO SEGMENTAL RESECTION

BRADLEY L. COLEY, M.D., AND NORMAN L. HIGINBOTHAM, M.D.
NEW YORK, N. Y.

IN recent years there has been a growing tendency on the part of those who treat neoplasms of bone, both benign and malignant, to rely more upon surgical measures and less upon roentgen therapy. The employment of the latter for tumors that are known to be radioresistant is at present restricted largely to inoperable cases or to those few patients who will not consent to surgery and it is conceded that the objective is palliation rather than cure. We know that worthwhile relief from pain and restraint of tumor growth may often follow the intelligent use of roentgen therapy.

With the present increasing preference for surgical measures there appears to be a definite trend in the direction of conservatism, especially in respect to the mutilating procedure of amputation. This does not mean that amputation is no longer regarded as the safest and most justifiable operation for the great majority of primary malignant tumors of bone. Rather it implies that in the past perhaps too little attention was paid to the possibility of selecting cases that might yield satisfactory results by a technic which, while it eradicated the disease locally, preserved all or most of the extremity and a good measure of function as well.

After devoting considerable thought to the possibilities inherent in procedures less radical than amputation we presented our conclusions in a paper; "Conservative Surgery in Tumors of Bone"; delivered at the Southeastern Surgical Congress in 1941. Further experience has but tended to strengthen our recorded convictions relative to the following:

(a) that there is a definite place for selecting a conservative rather than a more radical operation;
(b) that there are criteria which enable one to make a correct decision in the majority of instances;
(c) that there is a measure by which the surgeon can subsequently determine whether his initial decision was justified; and
(d) that if judgment is exercised the patient stands to benefit rather than to suffer from the surgeon's conservatism.

On the other hand, it would be regrettable if ill-considered and injudicious extension of conservative measures should lead to an over-enthusiastic adoption of less radical procedures, especially in circumstances where the latter offered a greater likelihood of a cure.

DEFINITION OF CONSERVATIVE SURGERY

For the purpose of this discussion we would define conservative surgery as an elective operation which either avoids amputation entirely or which

* Read before the New York Surgical Society, May 14, 1947.

places it at a lower level with greater prospects of improved function. As an example of the first, one might cite total excision of a scapula to avoid an interscapulothoracic disarticulation; and as exemplifying the second, the selection of an upper thigh level of amputation for a tumor of the lower femur —this in contrast to a hip-joint disarticulation. Other examples will be cited later.

FACTORS IN FAVOR OF A CONSERVATIVE PROCEDURE

In general one may state categorically that benign tumors almost always call for conservative measures. Tumors of border-line or of unquestioned, although low-grade, malignancy deserve consideration relative to the possibility of a less mutilating procedure than amputation. Here, other factors will often decide the proper selection.

Tumors which are medullary in origin and which do not appear to have penetrated through the cortex to present beyond the periphery of the bone are more prone to respond to a less drastic operation than amputation. On the other hand, typical "run-of-the-mill" osteogenic or chondro sarcomas, or those of great bulk, with wide extension beyond the normal confines of the bone and of high malignancy as determined by histologic study, are definitely unsuited to a conservative attack.

When considering the suitability of a more conservative approach the following criterion should be used: "Can the tumor together with sufficient tissue to prevent a local recurrence be completely removed, and if so, can a useful limb be maintained?" Once the decision to avoid an amputation has been made and the less mutilating measure carried out, subsequent events will prove the wisdom of the choice. Providing there is never any local or regional recurrence it may be regarded as having been a justifiable one even though distant metastasis ultimately occurs, for in the event of the latter even an amputation at the highest possible level would not have afforded any additional protection. However, if a local recurrence takes place then the choice may be regarded as having been ill-advised.

DESCRIPTION OF CONSERVATIVE PROCEDURES

1. *Curettage:* This is a widely used method of treatment for the following: Giant cell tumor, bone cyst, enchondroma, fibrous dysplasia and other lesions found beneath the cortex. By its means one can deal successfully with many benign tumors which formerly were sometimes subjected to amputation. The curetted cavity is usually cauterized with saturated solution of zinc chloride and irrigated thoroughly with saline before closure of the wound.

We have one five-year survival of a chondromyxosarcoma of the upper tibia in which after microscopic examination a curettage and bone graft was done deliberately; the patient remains well five years later with no evidence of a recurrence or metastasis;

In Case I, the procedure here would ordinarily have been thigh amputation.

2. *Partial Resection:* The acceptability of the principle of partial resection for benign bone tumors needs no further comment. Although for truly malignant tumors this measure may seem hazardous, in selected cases we believe it is indicated.

In support of this concept we cite a case of endothelioma of the upper fibula; and another of the lower fibula (Case II). In Case III both have remained free of disease for more than five years following partial resection of the fibula. Another noteworthy result of resection occurred in a pedunculated chondrosarcoma of the lower femur. In Case IV there was preservation of a normal limb and freedom from symptoms.

Owing to the prominent and virtually subcutaneous position of the clavicle, tumors which arise in this bone may be diagnosed more promptly and dealt with by partial or even total resection more readily than those having their origin in most of the other long bones. It is surprising how slight a functional impairment results even when the entire clavicle is removed.

3. *Segmental Resection and Massive Bone Graft to Repair Defect:* While the proper setting for resection of bone sarcomas is seldom encountered it would seem that surgeons have made little effort to utilize the measure even when an opportunity presented itself. Phemister stands almost alone among the living American surgeons who have made a determined effort to apply resection to carefully selected cases of primary sarcoma of the long bones. Indeed, he quotes figures from the records of the Bone Sarcoma Registry of the American College of Surgeons to show that of 701 cases of osteogenic sarcoma, only three of the 93 five-year survivals were treated by resection, and only one by resection and bone transplantation.

On the other hand, Phemister has practiced resection of the tumor-bearing segment and bone transplantation to replace the defect, in at least ten cases, not all of which have as yet been reported. Anyone who has studied Phemister's series must be impressed with the rare judgment he displayed in the selection of his cases combined with his technical skill in carrying out the extensive procedures. His series includes the following remarkable successes: —a ten-year survival of a patient with a resected osteogenic sarcoma of the upper right humerus who is still able to practice his profession of dentistry; an eight-year survival following resection of the upper five inches of the tibia for chondrosarcoma; a 12-year survival of a chondrosarcoma of the humerus treated by local excision and roentgen therapy. Even more remarkable are two femur cases that were treated by resection and utilization of massive transplants from both tibiae; one, a borderline giant cell tumor of the medial condyle remains well for three years and ten months after operation; the other, a central chondrosarcoma of low-grade malignancy remains well for four and one-half years after operation. One cannot refrain from extolling these results which demonstrate the valuable place held by resection in the treatment of borderline or slowly-growing malignant tumors.

Our experience with segmental resection and massive bone graft is limited to three cases; two of these involved removal of the middle third of the

humerus (Case V and Case VI), and in one (Case VII) the middle third of the ulna was resected. The lesions for which these operations were required were, thrice recurrent central chondroma, twice recurrent fibrous dysplasia and fibrosarcoma of low grade malignancy. The latter two cases are too recent to consider from the standpoint of end result. The first case, on the other hand, is well 11 years, with an excellent functional and anatomical result.

4. *Excision:* Some extremity bones may be completely excised together with the tumor, resulting in preservation of the limb and often only moderate functional impairment. This procedure may be applicable not only to benign tumors but to selected malignant ones as well. In the case of the latter, the more low-grade the malignancy the better the ultimate outlook—an observation applicable to more mutilating operations too. In this connection we would cite a case of chondromyxosarcoma of the scapula in which a partial and subsequently a total scapulectomy was followed by freedom from disease for a period of 11 years (Case VIII). In another noteworthy case (Case IX) total scapulectomy succeeded in eradicating a huge chondromyxosarcoma; however, later there developed pulmonary metastasis and a small local recurrence. The same result was noted in a case of angioendothelioma of the scapula (Case X) in a child, however, without local recurrence.

Owing to the extreme rarity of tumors of the patella, an opportunity to excise this bone is seldom afforded. However, in a case of malignant giant cell tumor of the patella (Case XI) an excellent local result was obtained; while pulmonary metastasis finally caused the patient's death three and one-half years later there was complete absence of local recurrence and during most of the interval between the operation and death, she was able to continue her work as a machine operator.

5. *Amputation:* At first, it may seem paradoxical to refer to an amputation as a conservative surgical measure; in a sense of course it is not. What is meant here is the substitution of a less radical for a more radical amputation, with the result that the patient is thereby better able to care for himself, to earn his living and to enjoy a more normal existence.

Reference to certain surgical texts reveals the usual admonition, *i.e.*, never to amputate for bone sarcoma through any portion of the bone involved. This, then, implies an obligatory hip disarticulation for all cases of osteogenic or chondro sarcoma of the lower end of the femur—a site in which the disease is most frequently found. We have long been convinced that with a careful selection of cases a high thigh amputation will prove an acceptable substitute in many instances. A recent study of 39 consecutive cases of osteogenic and chondro sarcoma of the lower femur in which a high thigh amputation was performed at Memorial Hospital in lieu of a hip-joint disarticulation, discloses that in 37 cases no stump recurrence took place; of the two in which this did occur (Case XII), one underwent a disarticulation at the hip and remained well for more than five years when last traced. Thus, in only one instance, or approximately 3 per cent, was the patient's chance of a survival theoretically diminished. On the other hand, 37 patients were afforded a sufficient stump

to provide them with an artificial limb and to remove them from the group of prospective crutch-users for the remainder of their lives. This, we regard as useful conservative surgery.

In another patient with a sarcoma of the lower fibula (Case XIII), the knee was preserved by an amputation performed five inches below the knee-joint; the survival period here is more than ten years.

Perhaps the most impressive case is that of a man (Case XIV) who had an osteogenic sarcoma of the proximal phalanx of the fifth finger of the right hand. Amputation of the fourth and fifth fingers and parts of the ulnar side of the hand left him with a useful member which enabled him to continue his occupation as a bus driver; he has remained well for nine years.

CONCLUSIONS

Conservative surgery for tumors of bone implies the substitution of some less radical procedure than amputation, or, if the latter is unavoidable, amputation at the lowest level compatible with safety.

Curettage, partial resection, segmental resection and excision are methods which may at times be used in lieu of amputation. If these procedures are successful in eradicating the primary tumor and in avoiding a local or regional recurrence, they may then be considered as wholly justified.

Certain histologic types and certain clinical and roentgenographic settings indicate the advisability or the inadvisability of attempting conservative measures.

High thigh amputation for osteogenic and chondro sarcoma of the lower femur may in selected cases be a safe substitute for hip disarticulation and offers greater advantages to the patients who survive.

It would seem to be worthy of our concentrated effort to perfect the operative treatment of bone neoplasms by every available means. One important advance might be the exercise of better care in the selection of cases in which less radical surgery would accomplish complete removal of the tumor with less mutilation, thus affording the patient a better opportunity to lead a more normal life.

CASE REPORTS

Case I.—M. K., female, age 31 years, was admitted on November 17, 1941, complaining of pain in the right knee of five weeks' duration. Examination revealed a slight swelling on the anterolateral aspect of the upper tibia. Operation, November 19, 1941; curettage of the tumor-bearing area of upper tibia and sliding bone graft from mid-tibia. Pathologic diagnosis: low-grade myxochondrosarcoma. *November 13, 1946,* five years later, patient presents no evidence of disease and films reveal a satisfactory appearance which has remained unchanged in the past four years. Function of the knee is unimpaired; an excellent result.

Case II.—W. B., male, age 14 years, was admitted on September 14, 1938, with a history of having injured his right knee in October, 1937, while playing football. This was followed in a week by the appearance of a swelling in the region of the head of the fibula, which slowly increased. On biopsy the pathologist reported endothelioma or small spindle cell osteogenic sarcoma but favored the former. Accordingly, the lesion was

treated with high voltage X-rays; a total of 1200R Units, delivered to each of three parts (anterior, posterior and lateral), and, in addition, the lower half of the fibula received 1200R Units through a lateral port. On November 21, 1938, the upper half of the fibula was resected and on pathological examination showed no evidence of residual tumor. *January 18, 1946* the patient reports that he is symptom free.

Case III.—B. C., male, age 22 years, was admitted on July 23, 1941, complaining of a lump on the outer aspect of the lower leg above the ankle. Doctor Ewing's diagnosis

FIG. 1A.—Case 3: Endothelioma of fibula.

FIG. 1B.—Five years after radiation therapy followed by segmental resection of fibula.

on a specimen obtained from a previous biopsy done elsewhere, was that of Ewing's sarcoma. Roentgen therapy was also given prior to admission. Operation, June 12, 1941; excision of lower fourth of fibula; stabilization of mortise with two vitallium screws. Pathologic diagnosis: bone radiation changes, but no residual tumor found. *July 31, 1946,* five years later, vitallium screws have been removed; there is a well-healed scar and excellent function of the left ankle. (Fig. 1).

Case IV.—H. B., female, age 40 years, was admitted on April 4, 1937, complaining of swelling of the left thigh, of two years' duration. Examination revealed an ovoid tumor, 8 x 9 cm., over the anterolateral aspect of the lower left femur. Sections from a previous biopsy performed elsewhere were reviewed by Doctor Ewing who confirmed the diagnosis of chondrosarcoma. Operation, April 5, 1937; excision of pedunculated tumor and primary wound closure. Pathologic diagnosis: osteogenic sarcoma, chondro type, very low-grade. *April 2, 1946,* nine years later, patient reports she has no complaints and has a full range of motion in the involved lower extremity.

A B

FIG. 2A.—Case 5: Central chondroma of humerus. Before operation.
FIG. 2B.—Recurrence after third operation.

FIG. 2C.—After segmental resection and massive tibial transplant to replace defect.

Case V.—A. C., female, age 27 years, was admitted on September 13, 1930, with a history of pain in the left arm of four years' duration. Examination revealed enlargement of the mid-portion of the left humerus, and roentgenograms disclosed a central radiolucent area, irregular in shape, occupying this portion of the bone. Conservative attempts (curettage), at removal were made in October, 1930, July, 1931, and in June, 1934. While the histologic report in each instance was that of benign central chondroma, each operation was ultimately followed by a return of symptoms. Accordingly, on February 18, 1937, a segmental resection of the mid-portion of the humerus, including the tumor-bearing area, with a safe margin on either side, was carried out; the resected portion was replaced by a massive tibial transplant mortised at either end (see Fig. 2C). This transplant ultimately united and the final result is shown in Fig. 2D). The patient is now well ten years since the resection during which interval she has been able to continue her work as a stenographer (Fig. 2).

FIG. 2D.—End result 9 years later showing complete consolidation of the transplant.

Case VI.—D. F., male, age 30 years, was admitted on December 21, 1939, complaining of pain in the right shoulder, of twelve months' duration. He gave a history of three episodes of traumatism to this area followed by pain. After the initial incident a fracture through a bone cyst was revealed. On examination, the right arm appeared swollen over the mid-portion. There was pain on attempted motion in any direction. The left arm had been amputated following an accident at the age of eight. The diagnosis following an aspiration biopsy on January 3, 1940, was that of "wall of bone cyst." Operation on the same date consisted of curettage of the cyst and implantation of a bone transplant from the tibia. Fairly satisfactory bone regeneration took place and the patient remained well until June 5, 1943, when on account of a recurrence of symptoms, a second operation was performed. This paralleled the first one. There was an additional period of three years of freedom from symptoms, followed by a recurrence and roentgenographic evidence of reactivity. A segmental resection was performed on April 8, 1946, a massive tibial transplant was doweled to fit in the medullary cavity at either end. In August, 1946, the transplant was fractured in its mid-portion. Examination in January, 1947, revealed definite evidence of callus formation; while solid bone union at the fracture site was lacking, the proximal and distal ends of the transplant were firmly united to the shaft.

Case VII.—R. R., male, age 38, was admitted on March 3, 1946, with a history of a swelling of the right forearm, which was first noticed in 1935, and steadily increased in size without any treatment. On March 6, 1946, the large, soft, part tumor was dissected free and removed with a 3½-inch segment of the ulna which was involved. A tibial trans-

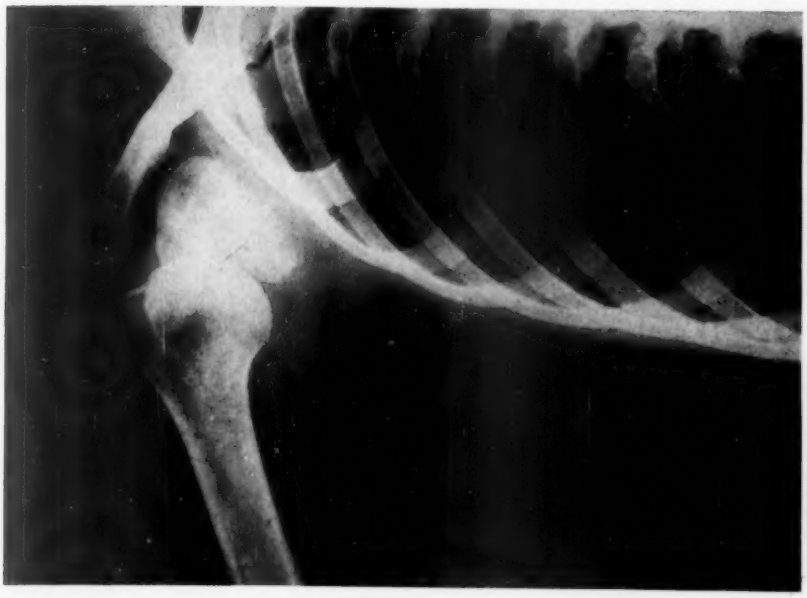


FIG. 3B.—Recurrence after partial resection of scapula.

FIG. 3A.—Case 8: Chondromyxosarcoma of inferior angle and axillary border of scapula.

plant, dowelled at either end, was used to fill the defect. Pathologic diagnosis was very low grade spindle cell non-metastasizing fibrosarcoma. On April 15, 1947, only ten months later, the condition of the graft was satisfactory and there was no evidence of recurrence.

Case VIII.—A. S., female, age 32 years, was admitted in December, 1934, for a tumor of the right scapula on which a biopsy had been performed in Philadelphia, two years previously. Microscopic report: Chondromyxosarcoma, recurrent. At that time an operation—excision of part of the scapula—was performed, followed by radiation therapy. Our operation consisted of sub-total excision leaving the glenoid and neck of the scapula. A recurrence took place within six months necessitating a total excision of the scapula on August 27, 1935. The pathologic diagnosis on both of these specimens was that of chondromyxosarcoma. Examination in May, 1942, revealed the patient in excellent condition; she had a good functional result with the exception of limited abduction of the arm. (Fig. 3).

FIG. 3C.—After total resection of scapula. Well 12 years later.

Case IX.—T. V. D., a 28-year-old Albino negro was admitted on April 6, 1934, with an enormous tumor of the left scapular region of two years' duration. There was a history of antecedent injury. Examination revealed a mass measuring 23 x 21 cm. over the left scapula; it was elevated 15 cm., beyond the normal body surface. A total scapulectomy was performed on April 21, 1934. Pathologic diagnosis: Spindle cell osteosarcoma. Death from pulmonary metastasis took place in early April, 1936; at this time there was also evidence of a small local recurrence in the operated area.

Case X.—J. C. V., male, age 9 years, was admitted on June 24, 1939, with a swelling of the scapula of 13 months' duration. Examination revealed a large tumor measuring

20 x 10 x 10 cm. A total scapulectomy was performed on June 28, 1939. Pathologic diagnosis: Angioendothelioma. Postoperative treatment by irradiation and Coley's toxins was carried out. The patient died on May 14, 1941, with intracranial metastasis, multiple subcutaneous nodules and pulmonary lesions, without evidence of local or regional recurrence.

Case XI.—H. A., female, age 47, was admitted on May 10, 1940, complaining of pain and swelling in the left knee over a period of two years, during which time she had sustained four falls on the knee, the latest one a month prior to admission. A cast had been applied. Examination revealed the affected patella to be three times the size of the normal one but it was freely movable and there was no skin attachment. Roentgenograms disclosed an osteolytic lesion involving the entire patella with accompanying soft tissue swelling. An aspiration biopsy was done and the pathologist reported: "Malignant tumor with a suggestion of malignant giant cell tumor." A total removal of the patella was performed on May 14, 1940, following which the pathologist reported: Malignant giant cell tumor. A course of Coley's toxins was given and the patient was discharged on June 21, 1940. She remained symptom-free, able to carry on her work as a machine operator, until May, 1943, when films revealed pulmonary metastasis, and she died on November 1, 1943, without evidence of local recurrence.

FIG. 4.—Case 13: Medullary and spindle cell osteogenic sarcoma, recurrent 10 months after resection of lower end of right fibula. Treated by radiation, Coley's toxins, then amputation at the site of election below the knee (instead of at or above the knee). Well 9 years later.

Case XII.—W. R., male, age 23, was admitted on November 22, 1935, complaining of a sore knee of six weeks' duration. On the direction of Doctor Ewing, he received a course of radiation therapy from November, 1935, to March, 1936. It was assumed that he had a giant cell tumor. No improvement followed, in fact he continued to grow worse and in August, 1936, a high thigh amputation was performed. Pathologic diagnosis: Osteogenic chondrosarcoma. Fourteen months later there was a recurrence in the soft tissues of the stump necessitating a hip-joint disarticulation on October 6, 1937. *April 17, 1946,* examination shows the patient to be in excellent condition, nine and one-half years after the second operation.

Case XIII.—M. B. W., female, age 26, was admitted on January 3, 1936, complaining of pain about the right ankle of 15 months' duration. She had been operated on elsewhere in March, 1935 (resection of lower end of right fibula), and a diagnosis of osteogenic sarcoma had been made. On admission she was given 40,000 millecuries of radium (element pack) and a course of Coley's toxins. On January 22, 1936, an amputation at the site of election below the knee was performed. Pathologic diagnosis: Medullary and periosteal spindle cell osteosarcoma. Examination in July, 1946, more than ten years later, revealed the patient in excellent condition; she has been able to earn her living as a clerk during this period (Fig. 4).

Case XIV.—W. C., male, age 30, was admitted on February 10, 1937, with a history of having injured the fifth finger of the right hand in November, 1936, when it was struck by a casting. There had been two operations for removal of tissue for diagnostic purposes. The first sections revealed chronic osteitis and the second were suggestive of giant cell tumor. However, the roentgenograms pointed more definitely to a diagnosis of osteogenic sarcoma. Operation performed on February 16, 1937, at Memorial Hospital consisted of partial amputation of the hand involving removal of the fourth and fifth fingers. The pathologic diagnosis of osteogenic sarcoma, low-grade, made by Doctor Stewart was confirmed by a number of the Committee of the Bone Sarcoma Registry. *Examination* on March 20, 1946, showed the patient to be in excellent condition with a useful hand more than nine years after the operation.

140 E. 54th St.
New York, N. Y.

THE CLOSURE OF COLOSTOMIES*

GEORGE BENTON SANDERS, M.D.
LOUISVILLE, KY.
HEINZ HAFFNER, M.D.
ST. LOUIS, MISSOURI
AND
ROBERT B. LYNN, M.D.
ALTON, ILL.

FROM THE SURGICAL SERVICE, VAUGHAN GENERAL HOSPITAL, HINES, ILLINOIS, AND THE DEPARTMENT OF SURGERY, UNIVERSITY OF LOUISVILLE MEDICAL SCHOOL, LOUISVILLE, KENTUCKY.

AS IN THE FIRST years following World War I, there has been a revival of interest in technics of colostomy closure. The magnitude of the recent conflict, and the greatly increased appreciation of the value of colostomy in the primary operative management of gunshot wounds of the colon, have afforded incomparable opportunities for evaluation of existing methods of making and closing colostomies.

Poor results attributable to the technic employed in closing a colostomy can be roughly grouped under three categories:

(1) Reopening of the closure with persistent fecal drainage.
(2) The occurrence of hernia at the site of closure.
(3) Pain at the site of closure, associated with varying degrees of obstruction to the fecal stream.

In the closure of any opening in the colon, whether traumatic or elective, certain fundamental surgical principles obtain. These are usually followed without question in cases of elective anastomosis of the bowel, but are often neglected in technics of colostomy closure.

(1) The blood supply to the bowel edges to be sutured must be preserved.
(2) Free edges of bowel must be accurately and snugly coapted without tension.
(3) Approximation of visceral peritoneal surfaces must be obtained if possible.
(4) The creation of obstruction or stenosis at the site of closure, either secondary to the technic of closure itself, or due to faulty repositioning of the sutured bowel, must be avoided.

If these principles are maintained, the closure of the opening in the bowel should remain secure. If they are neglected, no amount of chemotherapy or of reinforcement with fascial or other extraperitoneal layers will prevent leakage, infection, and reopening of the closure.

The avoidance of wound infection in an unavoidably contaminated field by refraining from extensive dissection of the various layers of the abdominal wall during the closure is also important. Such dissection tends to open up

* Presented at the meeting of the Central Committee on Fractures and other Traumas of the American College of Surgeons, January 15, 1946, Chicago, Illinois.

virgin tissue planes and spaces which have less resistance to infection than those adjacent to the colostomy. The reopening of an infected wound is most often followed, in short order, by reopening of the exposed suture line in the bowel itself. Preoperative preparation of the bowel with sulfasuxidine (succinylsulfathiazole or sulfaphthalidine (phthalylsulfathiazole) is undoubtedly of great value, but from our experience is not of supreme importance.

Intraperitoneal methods of closure greatly facilitate the proper observation of these surgical principles and particularly eliminate the danger of compressional or positional kinking of the sutured bowel, which is inherent in any extraperitoneal method of closure. Obstruction at the closure site by what

FIG. 1.—Lumbar colostomy made by exteriorizing damaged portion of upper cecum and first portion of ascending colon through wound of entrance of missile. Closure of this colostomy was very difficult and necessitated widespread mobilization and extensive dissection to provide a firm closure of the colon and a good repair of the lumbar tissues.

Warwick has termed "intraluminary kinking" remains a hazard in any type of closure, but can be reduced to a minimum by meticulous suturing or can be compensated for by a special type of anastomosis which will be described later.

MATERIAL

Seventy-two consecutive colostomy closures, done during a 15-month period, form the basis of the present study. The colostomies were all originally performed as adjuncts to the primary surgical management of gunshot wounds of the large bowel, ranging from the cecum to the terminal two inches of rectum. The types of colostomy encountered ran the gamut from orthodox to bizarre, as regards construction and site. Examples of lumbodorsal, flank, and low thoracic colostomies were included, as well as the more usual exteriorizations of riddled colonic segments, rotated colostomies, and partially retracted colostomies, (Fig. 1, 2). In one case, a transverse colostomy had been brought

out of the abdomen through a small stab wound low down in the left lower quadrant, (Fig. 3), and in another a sigmoid colostomy had been brought out through the internal inguinal ring and upper part of the left inguinal canal.

PREOPERATIVE CARE

Adequate information about the structural details of the colostomy were lacking in most of these cases. In no instance did we enjoy the privilege of closing a colostomy that we had made ourselves. Since all the colostomies in this series had been performed for penetrating wounds of the abdomen, involving not only the colon but other abdominal viscera and organs, the decision to

FIG. 2.—Flank exteriorization of damaged portion of descending colon just below splenic flexure. Proximal and distal stomas are indicated by pointers and have retracted about 1" below skin surface. The herniated mucosal mass of the riddled colonic segment contains four accessory openings. Colostomy has been brought out through wound of entrance of missile.

close a colostomy depended on the status of associated lesions in the small bowel, urinary tract, bony pelvis and distal colon. In many cases, extensive surgery was necessary for the cure or elimination of such lesions, usually before, but often at the time of closure of the colostomy. In some instances a poorly placed colostomy was closed and replaced with one more suitably located, which remained to be closed after further reconstructive surgery had been done upon the distal bowel. Such reconstructive surgery included transperitoneal closure of ureterosigmoid, vesico-rectal and hepatico-colic fistulae,

as well as the more usual and simpler closures of sacral, perineal and flank fecal fistulae (Fig. 4). In a number of cases, resection of extensive segments of colon, including the colostomy, was done (Fig. 5).

With a view to anticipating and reducing complications that might arise at, or after operation, an extensive program of preoperative study, preparation and evaluation was undertaken for each case (Table I).

OPERATIVE TECHNIC

The methods of closure employed ranged from simple extraperitoneal closure, to resection of the colostomy and adjacent four to eight inches of bowel, with end-to-end anastomosis. Only 12 extraperitoneal closures were

FIG. 3.—Transverse colostomy brought out through small oblique incision in left lower quadrant. Note massive edema, mucosal prolapse and rotation of colostomy (approximately 95°). Pointer is in proximal stoma.

done, and this method was abandoned early in the series. In 24 consecutive cases an intraperitoneal closure utilizing a modification of Pauchet's technic of anastomosis was employed with very satisfactory results. With the exception of the Pauchet closures and four cases of resection and end-to-end anastomosis, the remainder, or 32 cases, were closed by an intraperitoneal technic similar to that described by Dixon and Benson (Fig. 6). The surgical principles previously outlined were scrupulously followed in all closures but two, both done by the extraperitoneal route. These two closures reopened for a short time, but later closed spontaneously without the necessity for further surgical intervention.

TABLE I.—*Routine Preoperative Colostomy Study**

I. In addition to the usual laboratory work, the following should be done:
   (1) Prothrombin time.
   (2) Vitamin C.—blood level.
   (3) Plasma chlorides.
   (4) Plasma-protcins.
   (5) NPN.
   (6) Weigh the patient.

II. In addition to the ordinary physical examination, the following should be done:
   (1) Digital rectal examination.
   (2) Digital colostomy examination (under pentothal anesthesia if necessary).
   (3) Examine for skin excoriation around colostomy. (If present, Kaolin paste should be applied twice daily.)
   (4) Tap water enema, 500 cc. through distal loop. If any debris exists in distal loop, enema should be given daily until cleared
   (5) Procto-sigmoidoscopy. *Precaution*: In injuries to the pelvic colon, especially following buttock or perineal wounds, the bowel is often fixed by scar and inflammatory tissue making the passage of the sigmoidoscope difficult or impossible, and *always hazardous*. *Extreme gentleness* must be observed for the avoidance of both pain and serious trauma to the colon.

III. (1) Educate patient, if not already trained, to care for his own colostomy.
   (2) Daily bath.
   (3) 2000 cc. tap water enema through proximal loop at approximately same time every third day until preoperative sulfasuxidine is started.
   (4) Kaolin paste around stoma if *any* excoriation is present.
   (5) High caloric—low residue diet.
   (6) Supplementary vitamin therapy.

IV. Special studies:
   (1) Open film of abdomen for retained foreign bodies in *all* cases.
   (2) Intravenous pyelogram. *In every case.*
   (3) Barium enema. (Don't give barium to a patient going on furlough unless 2-3 days are spent thereafter *in the hospital* thoroughly evacuating barium from distal loop. Because of the peculiar physiological status of an inactive distal loop, barium may be incompletely evacuated and develop into a considerable plug.)
   (4) Weigh patient once a week.
   (5) Cystoscopy, retrograde pyelography, GI series, cholecystography, etc., will be done according to indications in each case.

   PRECAUTIONS:
   (1) *Don't* send any patient on furlough with barium still in the distal loop.
   (2) *Don't* send any patient on furlough with an *internal* fistula, without a *thorough* workup including consultations; (for example, urologic consultation in the case of urinary-fecal communications).
   (3) Be sure each furlough patient understands the care of his colostomy, including diet, cleanliness, enemas, etc.
   (4) *Don't* send any patient on furlough who has skin excoriation around colostomy.

V. Chemotherapy:
   (1) Sulfasuxidine .025 Gm. per kg. daily in four divided doses, and Synkayvit (synthetic vitamin K) 5 mg. TID by mouth, for at least six days. All enemas, and colonic irrigations, should be withheld during sulfasuxidine administration.
   (2) Prothrombin time before starting sulfasuxidine, and on day prior to operation.
   (3) If skin excoriation develops around the colostomy during sulfasuxidine preparation, notify surgeon promptly; instruct patient to bathe several times daily, and apply kaolin paste more frequently.
   (4) Tap water enema (1,000 cc.) to both loops on night before operation.
   (5) Paregoric, 8 cc. night before operation and repeat in A.M. before operation.

VI. *Postoperative Routine.*
   (1) Full liquid diet as tolerated, upon return from operating room.
   (2) Mineral oil, 15 cc. Q.I.D.
   (3) Rectal tube, q. 2. hrs.
   (4) Patient may be ambulatory on the first postoperative day.
   (5) Soft diet, first or second postoperative day, as tolerated.
   (6) Regular diet as soon as spontaneous bowel movements appear.

   Note—Sulfasuxidine is not to be continued postoperatively except in special cases involving extensive bowel resection, or upon the individual recommendation of the surgeon.

* The outline as given above was published on each surgical ward for the guidance of the ward personnel. Apologies are tendered for the obvious naiveté of the instructions.

All operations were done under spinal anesthesia. A simple preparation of the operative field with soap, water, ether, and a suitably tinted skin antiseptic was found to be completely adequate. Irrigation of the colostomy on the operating table, the use of gauze plugs, and other complicated procedures described elsewhere, were not employed.

The operative incision was closed without drainage in all but five cases. In three of these the technic of delayed closure, described by Coller and Valk, and by Pemberton, was employed. In one case, a Penrose tube was left for

FIG. 4.—Lipiodol injection made solely through sacral opening of uretero-sigmoid fistula, showing sigmoid and ureteral connections. The left hydronephrosis subsided with the passage of four calculi, following dilatation and catheter drainage of the left ureter and kidney pelvis. Cure of the fistula obtained by establishment of Devine colostomy in transverse colon, closure of sigmoid colostomy, and finally, transperitoneal closure of fistulous openings in recto-sigmoid and left ureter. The left kidney was preserved.

36 hours down to the site of closure of an associated hepatico-colic fistula. In another case, in which the wound of entry had been used to bring out the colostomy from the abdomen, an inevitable subcutaneous dead space resulted, which was drained for 36 hours by a Penrose tube.

CHEMOTHERAPY

In a majority of cases preoperative preparation of the colon for six days with sulfasuxidine (succinylsulfathiazole) and a low residue diet was carried

out. At first, sulfasuxidine was given on a basis of .25 Gm. per kg. of body weight per day in four divided doses, as recommended by Poth and Knotts. Later, four daily doses of two or three grams each, depending on the approximate weight and size of the patient, were routinely employed. Enemata and colon irrigations were withheld during sulfasuxidine administration. In only three cases involving fairly extensive bowel resection was sulfasuxidine continued postoperatively. After the appearance of hemorrhagic phenomena in

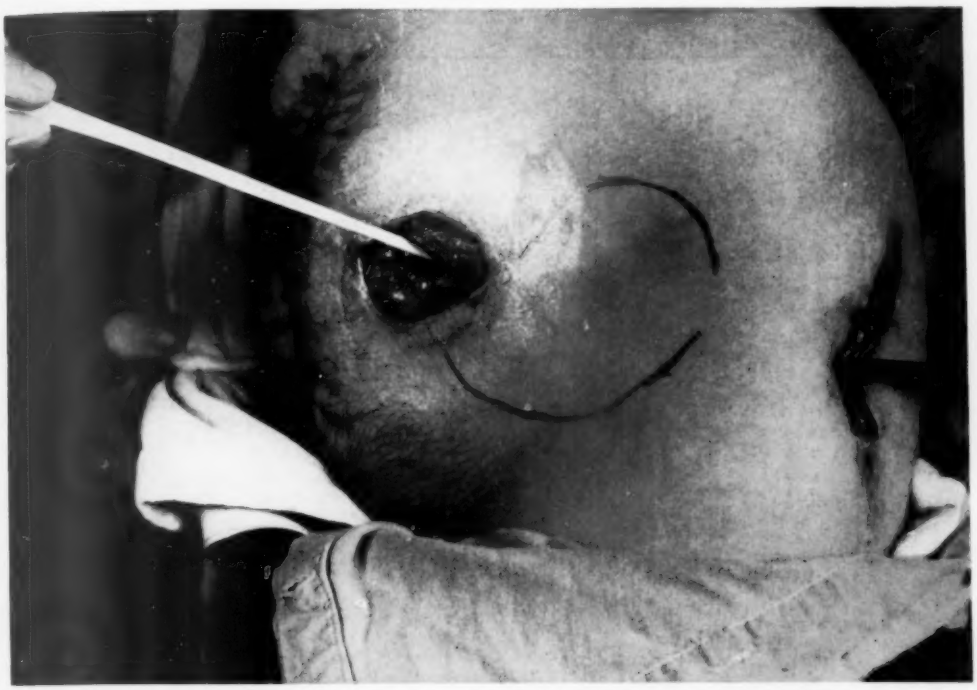


FIG. 5.—Case in which sniper bullet transected the sigmoid, perforated the ala of the left ilium and exited near the left buttock. Transected sigmoid brought out through wound of entrance as a colostomy, rotated 120°, with the development of a fecal fistula from the distal loop, and a large iliac abscess, which is outlined on the skin. The skin discoloration over the abscess can be seen. Pointers are in the internal and external openings of the fecal fistula which traverses the ala of the left ilium. Cure involved establishment of Devine colostomy in transverse colon and drainage of the abscess; later, resection of involved sigmoid and end-to-end anastomosis.

two instances, synthetic vitamin K was given by mouth during sulfasuxidine administration to all subsequent patients. The topical application of crystalline sulfanilamide to the suture line in the bowel and to the layers of the operative wound was carried out in a few cases, and then discarded as unnecessary. In four cases no sulfonamide therapy whatsoever was employed.

POSTOPERATIVE CARE

All patients were given a liquid diet upon returning from the operating room, and most had progressed to taking a regular house diet by the third or

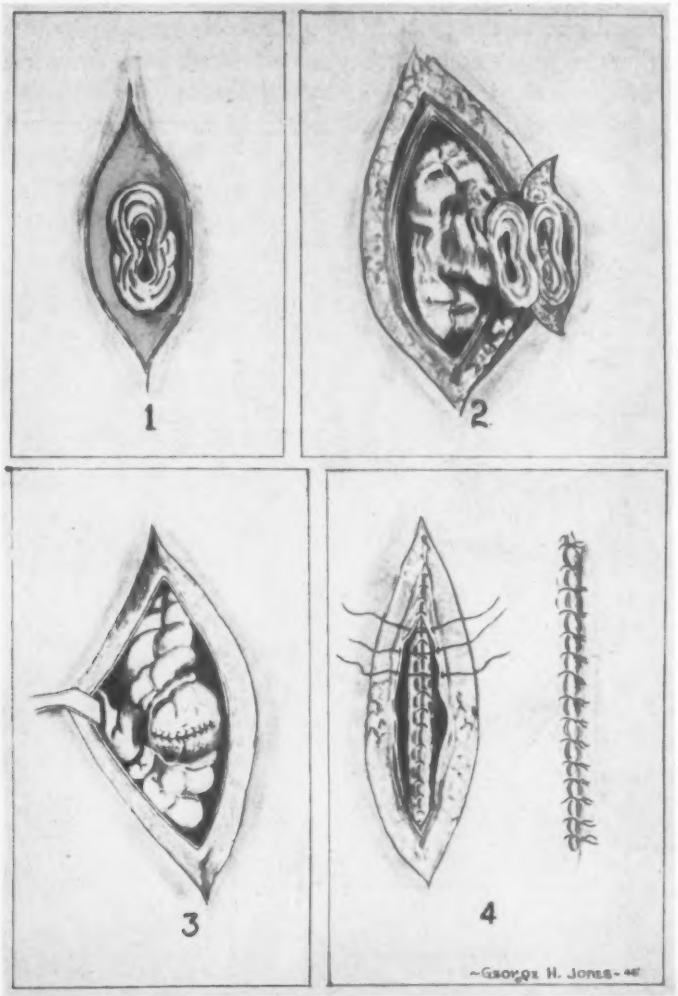


FIG. 6.—Technic of Simple Intra-Peritoneal Colostomy Closure (After Dixon and Benson)

(1) Elliptical incision encircling stoma. (Spur has been previously crushed)

(2) Incision carried down through all abdominal layers, opening peritoneal cavity. Mucocutaneous cuff of stoma resected.

(3) Transverse closure of colostomy, using two layers of sutures.

(4) Wound closed in layers without drainage, using interrupted sutures of fine cotton or silk. Topical sulfonamide is not employed.

fourth postoperative days. Parenteral fluids, blood and plasma transfusions, were rarely necessary postoperatively. Periodic insertion of a rectal tube was begun as soon as the patient returned from the operating room in order to

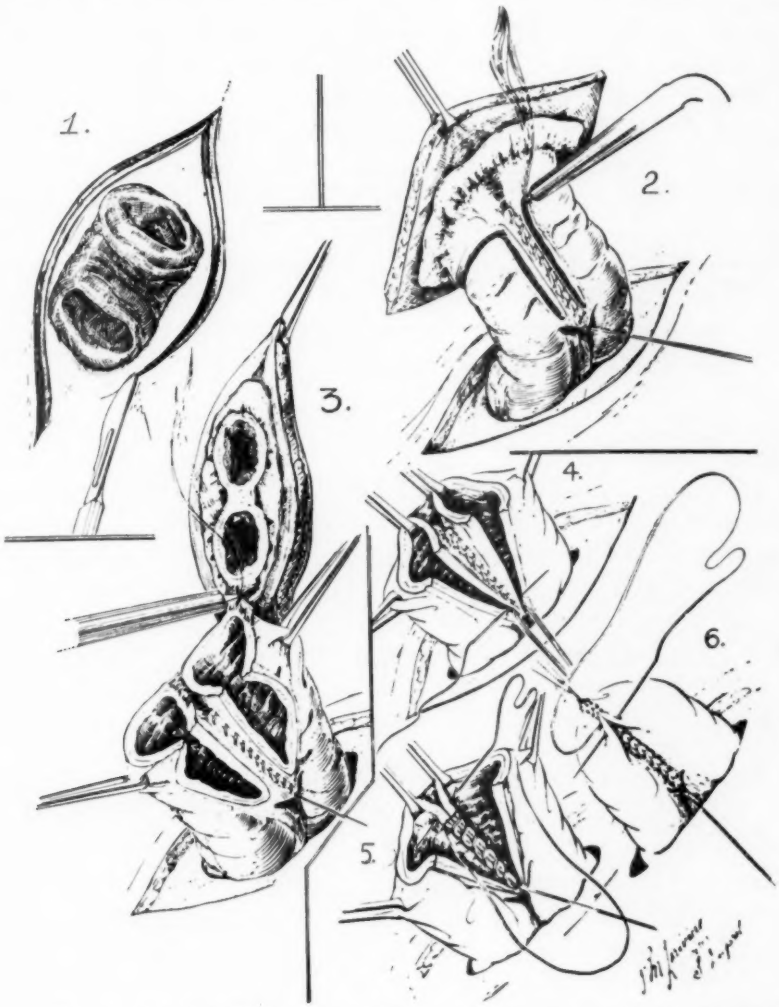


FIG. 7.—Pauchet Technic of colostomy closure. The cautery is not used in our modification of this procedure. The colostomy stoma and adherent skin cuff are excised with the scissors. The vertical incision in the long axis of each bowel limb is made, also with scissors, from the stoma downward, instead of as shown. The continuous suture shown in 5 is usually continued down the lateral aspect of the anastomosis as a continuous Connell stitch in our technic. Interrupted Halsted sutures of fine black silk are substituted for the continuous Lembert suture shown in 6. (Reproduced by permission of the publisher from Maingot, ABDOMINAL OPERATIONS, Vol. II, Page 1334, D. Appleton-Century Co., New York)

decompress the colon distal to the closure. This was continued until the first bowel movement, which was usually on the third or fourth postoperative day. All patients were ambulatory by the fifth or sixth postoperative day.

PAUCHET CLOSURE

In 24 cases a modification of Pauchet's technic of intraperitoneal colostomy closure was done.

This procedure embodies largely the principle of the Finney pyloroplasty, and briefly consists in encircling the colostomy stoma by an elliptical skin incision, leaving a cuff of skin about one-quarter inch around the mucosal edge. The incision is deepened in an anatomic manner by sharp dissection through all the layers of the abdominal wall down to the peritoneum, which is then deliberately opened along the medial aspect of the colostomy. The peritoneal incision is continued by sharp dissection so that it completely encircles and frees the afferent and efferent limbs of the colostomy. With gentle traction on the bowel, further mobilization is continued as far as is necessary to provide an adequate length of bowel for the anastomosis, and to permit, if necessary, resection of the colostomy or of segments of bowel deformed by secondary fistulas, extensive scarring or granulomatous masses. Proper mobilization permits complete delivery from the abdominal cavity of the afferent and efferent limbs of bowel to be used in the anastomosis. The wound edges and the peritoneal cavity are protected by two large saline packs tucked snugly down into the wound around the bowel. All subsequent surgical procedures are then carried on entirely outside the abdominal cavity and the operative wound. The anastomosis is performed (Fig. 7) after such complications as bowel rotations and interposition of small bowel or omentum, *etc.*, are corrected and after resection of undesirable segments of bowel has been completed. Upon completion of the anastomosis, the bowel is carefully replaced within the peritoneal cavity so as to avoid twisting or kinking, and the wound is then closed in layers without drainage.

At first we employed the method for the closure of colostomies whose defects or complications prohibited spur crushing and simple intraperitoneal closure. The good results and smooth postoperative course in these first few cases, and the obvious advantage to our patients of avoiding the time lost in a spur crushing procedure, impelled us to adopt the method as the procedure of choice in closing subsequent colostomies. The advantages of the method are, in general, those of any intraperitoneal type of closure in avoiding positional and compressional kinking of the bowel at the site of the closure; in providing for an adequate repair of the abdominal wall in which the development of hernia subsequently is extremely unlikely; and in the general security of the closure itself. In addition to these advantages, the method insures a very generous lumen at the site of anastomosis, even though a firm, leakproof, three-layer anastomosis is done, turning in a generous cuff of bowel wall. By this method, the development of obstruction at the site of closure from either extrinsic or intrinsic causes, is completely avoided or compensated for to a degree not attainable with end-to-end anastomosis, and the other prime requisites for a successful closure already mentioned are ensured.

The postoperative course of these 24 patients was very smooth. A full liquid diet was taken by all patients in this group upon their return from the

operating room. All patients were ambulatory by the first postoperative day. Flatus was passed freely per rectum on the first or second postoperative day, normal bowel movements occurred on the second or third day, usually without enemata or catharsis, and all patients were taking a regular house diet by the third day. Gas pains, distention, vomiting, the withholding of food, the use of suction decompression, parenteral fluids, and other postoperative nuisances, were conspicuously absent. There were no wound infections, wound reactions, or failures of the closure, in this group. Barium studies of the colon at three

FIG. 8.—Barium Study of Colon four weeks after Pauchet closure of Colostomy.

to four weeks postoperatively revealed adequate, or even generous lumens in each case, without evidence of postoperative stricture or stenosing deformity (Fig. 8).

RESULTS

The results in 72 consecutive colostomy closures are shown in Table II.

COMMENT

There were no deaths. Failure of the closure occurred in two cases, early in the series, due to faulty technic. In these two cases, we presume that some degree of wound infection took place. This, however, was completely masked

or overshadowed by the reopening of the closures, on the fourth and fifth days, respectively, which was of a somewhat cataclysmic nature.

There were no wound infections or "reactions" in the remaining 70 cases. All incisions appeared to be healing well without reaction on the sixth postoperative day, at which time skin sutures were removed. Subsequent healing was uneventful and resembled that expected in clean elective incisions.

Following the appearance of hemorrhagic phenomena in two patients on the second postoperative day, due to hypoprothrombinemia, synthetic Vitamin K was given by mouth during sulfasuxidine administration to all subsequent patients. Routine studies of prothrombin time, done the day before sulfasuxidine preparation was begun, showed high normal values in these two patients.

TABLE II.—*Results in 72 Consecutive Closures of Colostomies Done for Battle Wounds of the Colon*

	Number	Per Cent
Failure of closure	2 (Closed spontaneously later)	2.8%
Wound infection	2(?)	2.8%
Healed by 14th postoperative day	70	92.2%
Persistent sinus with drainage	0	.....
Pain at site of closure	0	.....
Hernia at site of closure	0	.....
Stenosis at site of closure	1 (following end-to-end suture)	1.4%
Obstructive symptoms at site of closure	0	.....

With the appearance of hemorrhagic phenomena postoperatively, namely, rectal bleeding, the prothrombin time was again determined in these two patients and found to be less than 10 per cent of normal. In both cases, bleeding stopped within three hours following the intravenous administration of large doses of Vitamin K and the restoration of normal prothrombin values. Although acceptable proof is lacking, we feel that the marked reduction in vitamin K- synthesizing colonic bacteria brought about by sulfasuxidine, was at least partly responsible, and suggests interesting possibilities for clinical investigation.

It is difficult for us to evaluate the clinical results of sulfasuxidine preparation of the bowel from our experience with such a small series of cases. At least a dozen closures were performed without sulfasuxudine preparation, and it appeared to us that their postoperative course was fully as smooth as regards wound healing, absence of febrile reaction, minimal postoperative discomfort, gas pains, *etc.*, as those in which sulfasuxidine was given preoperatively. At the operating table, however, the advantages of sulfasuxidine preparation were more clearly demonstrated by the scrupulous cleanliness and complete absence of fecal debris in the colon thus prepared. From these observations we have concluded that sulfasuxidine preparation is of great value in reconstructive surgery of the large bowel, including colostomy closures, but is certainly not indispensable.

SUMMARY

Experience with 72 consecutive colostomy closures has resulted in a decided preference for a method of colostomy closure which will provide the following:

1. As nearly anatomic a reconstruction of the colon and abdominal wall as is possible, namely, an intraperitoneal type of closure.

2. A technic of closure which obviates the wastage of time and the not too remote dangers attending a preliminary spur crushing procedure.

3. A type of intestinal anastomosis which will allow the surgeon considerable freedom in suturing so that he may make a two, or even three, layer closure of great firmness, turning in a sufficient cuff of bowel wall to ensure excellent peritoneal coaptation, and yet at the same time leaving a sufficiently large lumen at the site of closure which will not under any circumstances become stenotic, either due to immediate postoperative edema, or later from cicatricial contraction.

In the main, end-to-end anastomosis, with or without actual resection of the colostomy itself, satisfies these requirements fairly well. Nevertheless, it has been our experience in a significant number of cases, that, with this method, immediate postoperative edema has sufficiently compromised an otherwise adequate lumen, so as to endanger the integrity of the suture line or to cause postoperative discomfort, cramps and other nuisances. Consequently, our decided preference is for the Pauchet type of closure, which we have come to employ almost exclusively for the closure of colostomies in the transverse, descending, and sigmoid colons. In our experience with this type of closure, withholding of food postoperatively is unnecessary, postoperative discomfort is minimal, early ambulation is accomplished readily, wound infection, leakage or failure of the closure, and obstructive symptoms, either early or late, are thus far unknown.

REFERENCES

1 Coller, F. A., and W. L. Valk: The Delayed Closure of Contaminated Wounds. Ann. Surg., **112**: 256, 1940.

2 Coller, F. A., and H. H. Vaughan: Treatment of Carcinoma of the Colon. Ann. Surg., **121**: 395, 1945.

3 Dixon, C. F., and R. E. Benson: Closure of Colonic Stomas. Ann. Surg., **120**: 562, 1944.

4 Dor, M. J.: La Fermeture Des Anus Iliaques Gauches. Jour. de Med. De Paris, **37**: 659, 1938.

5 Finochietto, R.: Colostomia, Seccion de Espolon. La Prensa Medica Argentina, **46**: 2206, 1943.

6 Horsley, G. W., Lt. Col., M. C.: Surgery of the Colon as Seen in a General Hospital. Med. Bull. of the Med. Theatre of Op. **3**: 45, 1945.

7 Howser, I. W.: An Improved Technique for Closure of a Loop Colostomy. Am. J. Surg., **2**: 187, 1944.

8 Keene, C. H.: Colostomies. Bul. U. S. Army Med. Dept., **86**: 115, 1945.

9 Lockhart-Mummery, J. P.: Discussion on Methods of Making and Closing Colostomy Openings. Proc. Roy. Soc. Med. Lond., **10**: 135, 1916–17.

10 *Idem:* The Closure of Colostomy Openings. Lancet, **1**: 554, 1917.

[11] Mayo, C. W., and C. P. Schlicke: That Hazardous Eminence, the Colostomy Spur. Am. J. Surg., **58**: 29, 1942.

[12] Maingot, R.: ABDOMINAL OPERATIONS, Vol. II, p. 1334–1335. New York City, D. Appleton-Century Co.

[13] Pauchet, V., and LeGac, P.: Fermeture d'un Anus Artifiel Gauche Consecutif A Une Colectomie Gauche Segmentaire. La Pratique Chirurgicale Illustree., **19**: p. 130, E. Doin et Cie., Paris.

[14] Pemberton, J. de J., and B. M. Black: Delayed Closure of Incisions Made at Closure of Colonic Stomas. Surg. Gyn. & Ob., **76**: 385, 1943.

[15] Poth, E. J., and F. L. Knotts: The Clinical Use of Succinyl-Sulfathiazole. Arch.-Surg., **44**: 208, 1942.

[16] Poth, E. J.: Succinyl-Sulfathiazole and Phthalyl-Sulfathiazole in Surgery of the Colon. Surg., **17**: 773, 1945.

[17] Sanders, G. B., and P. H. Halperin: Experiences with the Pauchet Technique of Colostomy Closure. Surg., **20**: 82, 1946.

[18] Shallow, T. A., S. A. Eger, and W. J. Tourish: An Improved Method for Extraperitoneal Closure of Colostomy. Surgery, **18**: 466, 1945.

[19] Warwick, W. T.: Closure of Colostomy. Practitioner, **151**: 156, 1943.

University of Louisville
Department of Surgery
Louisville, Kentucky

MODERN CONCEPTS OF URETERAL CALCULI

CHARLES C. HIGGINS, M.D., AND J. G. WARDEN, M.D.
CLEVELAND, OHIO

IT IS NOW generally conceded that ureteral calculi are originally formed in the kidney and then pass into the ureter. Calculi which develop *ab initio* in the ureter are rare, as the smooth mucosal lining is constantly being washed with urine, and because gravity exerts a pulling force on crystalloid accumulations of stones. However, cases have been reported in which anatomic or pathologic areas of stasis (sacculations or diverticula) are undoubtedly responsible for the formation of ureteral calculi.

Available reports cite instances in which ureteral stones have formed in connection with ureteroceles, neoplasms, ureters with blind endings, or ectopic ureters. This series of 256 cases is reviewed not only to ascertain general information governing ureteral calculi, but also to compare the type of treatment instituted with that of previously reported series. This presentation is a supplementary report on ureteral calculi treated at Cleveland Clinic from 1939 to 1945.

Etiology.—Inasmuch, as ureteral calculi are usually formed in the kidney, the factors governing the formation of renal calculi merit consideration. It is generally accepted that no single etiologic factor is responsible for the formation of the calculi. Thus, if the causative factors in the individual case are not determined and eradicated, recurrent stone formations will ensue. It is evident that only by intensive preoperative investigation and diligent postoperative management can the morbidity of this disease be reduced.

In view of our present knowledge of calculus formation, the following factors must be studied: (1) hyperparathyroidism; (2) vitamin-A deficiency; (3) stasis; (4) metabolic diseases; (5) focal infection; and (6) infections of the urinary tract.

Each etiologic factor warrants investigation in order that, if present, it may be corrected at the time of operation or during the period of postoperative observation.

Age Incidence.—Stone in the ureter is essentially a disease of middle life. In this series, 69 per cent occurred between the ages of 21 and 50 (Table I).

TABLE I

AGE INCIDENCE

Age	Cases
1–10 years	0
11–20 years	2
21–30 years	31
31–40 years	55
41–50 years	91
51–60 years	58
61–70 years	18
Over 70 years	1

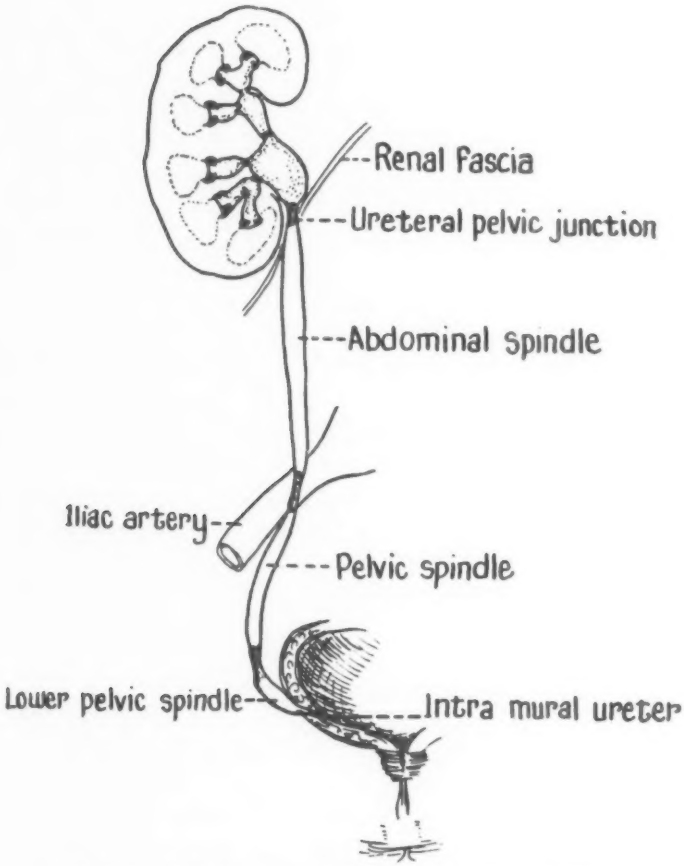


FIG. 1.—Points of constriction in the normal ureter.

The youngest male was 20 and the youngest female 22 years of age. The oldest male was 72 and the oldest female 61 years of age. These results agree with a series of 122 cases reported by Mathe (Table II).[1]

TABLE II

AGE INCIDENCE OF MATHE'S CASES

Age	Cases
0–10 years	0
10–20 years	6
20–30 years	13
30–40 years	28
40–50 years	34
50–60 years	24
60–70 years	17

Sex.—The incidence of ureteral calculus is much greater in men than in women. Ravich[2] states that 69.8 per cent occur in men and 30 per cent in women. Bumpus and Scholl[3] observed 68 per cent in men and 32 per cent in

women. In a series of 350 cases reported by the author in 1939, 79.7 per cent were in men and 20.3 per cent in women.[4] In this series of 256 cases, 79 per cent were in men and 21 per cent in women.

Side Involved.—The occurrence of ureteral calculi on the left and right sides is approximately equal. Kretschmer[5] observed that in 500 cases, 45.8 per cent were on the right side and 51.8 per cent on the left side. In our series of 350 cases previously reported, 46 per cent were in the right ureter and 54 in the left ureter. In this series of 256 cases, 47 per cent were in the right and 53 per cent in the left ureter. Bilateral ureteral calculi occur in 1.7 to 3.6 per cent of cases.

Location of Calculus.—The majority of calculi become impacted in the pelvic portion of the ureter. As a general rule the descent of the stone is arrested at one of five points in the ureter. These points are the normal locations of constriction to be found in the ureter (Fig. 1), namely; (1) at or just below the ureteropelvic junction; (2) at the point where the ureter crosses the iliac vessels; (3) at the base of the broad ligaments in the female and of the vas deferens in the male; (4) at the point where the ureter enters the external muscular layer of the bladder; and (5) at the ureteral orifices. In our series of 350 cases the location was as shown in Table III.

TABLE III

LOCATION OF CALCULI

Right upper ureter	14 cases
Left upper ureter	16 cases
Right midureter	21 cases
Left midureter	22 cases
Right lower ureter	128 cases
Left lower ureter	143 cases
Bilateral calculi in 6 cases:	
Right and left lower ureter	3 cases
Right lower ureter and left upper ureter	1 case
Right midureter and left midureter	1 case
Right midureter and left lower ureter	1 case
In this series of cases the following location was noted:	
Right upper ureter	15 cases
Left upper ureter	22 cases
Right midureter	7 cases
Left midureter	12 cases
Right lower ureter	89 cases
Left lower ureter	99 cases
The location of the calculus was not stated in 12 instances.	

SYMPTOMATOLOGY

The symptoms produced by a stone in the ureter may so closely simulate those produced by a stone in the kidney that roentgenologic study may be necessary to establish the correct diagnosis. The position of the calculus, the presence or absence of obstruction or infection, and the movement of the stone may influence the symptoms.

Pain was the predominant symptom in this series. It occurred as colic in 151 (59 per cent) of cases, and as unilateral costovertebral-angle pain in 51 (20 per cent) of cases. Indefinite abdominal discomfort was present in 57 (22.7 per cent) of cases, and nausea and vomiting in 94 (36 per cent).

In the 350 cases previously reported, 20 per cent presented symptoms not referable to the urinary tract in contrast to 22.7 per cent above. In the previous series, in 14 per cent of the cases the pain was referred to the upper quadrants of the abdomen, and in 6 per cent the pain was referred to the right or left lower quadrants.

Bumpus and Thompson[6] found that the appendix had been removed in 26.8 per cent of the 138 cases of ureteral calculi prior to establishing an accurate diagnosis.

Calculi in the upper ureter produces pain either as colic radiating around the abdomen to the genitalia or by obstruction producing a fixed sharp or dull pain in the posterior renal area. Stones in the pelvic portion of the ureter may produce colic, obstructive symptoms, and also pronounced vesical symptoms. In one patient the only complaint was severe pain in the testicle, others had pain referred to the perineum, rectum, medial portion of the thigh, and localized pain medial to the knee joint.

During their attacks nearly half of the patients noted frequency. Urgency was present in 31.3 per cent of the 256 cases, and many of the patients gave a history of vague abdominal pains associated with frequency. This led to complete urologic examination and finding of a calculus.

Urine examination revealed microscopic hematuria in 212 (82.8 per cent) and gross hematuria in only 94 cases (36.7 per cent). Microscopic pus was present in the urine in 226 (89 per cent).

Carp[7] states that in a study of 100 patients with ureteral calculi 93 per cent developed a leukocytosis. Of this group 20 per cent had white blood cell counts of from 15,000 to 30,000; 42 per cent from 10,000 to 15,000, and 31 per cent from 7,000 to 10,000. He states that this finding is of great significance and should be incorporated in the classical picture of ureteral calculus.

Roentgenographic refinements in technic have made the number of undiagnosed ureteral calculi exceedingly small. Peterson and Holmes[8] found in 100 cases that 96 per cent were diagnosed by roentgenologic study. The most frequently overlooked calculi were located in a small area medial to the spine of the ischium and just above a line joining the lowest part of the ischial spines.

In this series of 256 cases 98.4 per cent of the stones were demonstrated roentgenologically. Two hundred and thirty-seven were visualized on the initial roentgenogram, and 15 additional calculi were shown by the use of radiopaque dye.

Stones lying low in the ureter render cystoscopic examination a valuable adjunct in diagnosis. A calculus approaching the bladder will make typical changes of edema about the ureteral orifice, a definite bulging may be noted, a gaping orifice, or the calculus in the orifice may be observed.

Other corroborative evidence includes striking an obstruction with a ureteral catheter (plain or wax-tipped) and the hydronephrotic drip of urine. It is also suggestive after a catheter has passed a grating obstruction, followed by relief of pain in the renal area.

During the present decade intravenous urography has become an important

diagnostic aid. In addition to demonstrating opaque and nonopaque stones a physiologic picture of renal function is secured, thereby giving an index of the proper therapeutic course to be followed. By the employment of intravenous urography we can determine the status of the kidney above the calculus, *i.e.*, the degree of hydronephrosis, if present, and determine if complete or only partial obstruction is being produced by the stone. It also obviates the chances of dislodging the stone and forcing it back into the renal pelvis if a catheter (ureteral) is introduced through the cystoscope.

TREATMENT

Few urologic problems require consideration of so many factors as does an obstructing ureteral calculus. Whether or not to operate and relieve the obstruction immediately or to manipulate and possibly subject the patient to a period of disability, painful colic, and possible febrile reactions is a question arising in every case. Likewise should a period of watchful waiting be pursued. What are the factors to be evaluated in deciding whether or not the patient should be carefully watched in anticipation of spontaneous expulsion of the stone, manipulation procedures should be recommended, or surgery advocated?

(1) *Economic Status and Occupation:* As the economic status of the patient and his occupation may influence the procedure to be advocated for medical problems extraneous to the urinary tract, so may it influence the type of therapy to be recommended in a patient with ureteral calculus.

A sudden attack of colic in persons working with machinery, airplane pilots, engineers, *etc.*, may not only endanger their lives but also those dependent upon them. A laborer in whom a stone impacted in the upper ureter passes slowly down the ureter, its progress at times being arrested for varying periods of time, and who is subjected to repeated attacks of colic may be restored to gainful occupation more quickly by the surgical removal of the stone through a muscle-splitting incision.

There are, likewise, occupations which require considerable exertion and expenditure of energy and provoke frequent attacks of colic in the patient, who may, due to his financial status and obligations, require more immediate relief of symptoms.

(2) *The Size of the Calculus:* This is of considerable importance, but we are of the opinion, as are others throughout the literature, that of equal importance is the size of the ureter below the stone. It is a relatively easy matter to pass catheters or extractors along the sides of a stone in a large ureter, and often impossible to pass a catheter by a small stone in an undilated ureter. As a general rule, the larger the calculus the less likely it is to pass spontaneously, and more frequently will manipulative efforts fail to succeed.

Joly[9] has stated that patients passing stones at varying intervals of time are able to pass progressively larger calculi. Thompson and Kibler[10] state that in 361 cases of ureteral stones in which manipulative procedures were used, in 46 per cent the stones measured 1 to 2 cm., in 19 per cent the

diameter varied from 0.5 to 1 cm., and in 20 per cent the diameter was less than 0.5 cm. In our experience stones larger than 1.5 cm. in diameter are rarely amenable to transurethral manipulation.

(3) *Status of Kidney above the Calculus:* Final acceptance of any method of ureteral calculus therapy should have as its prime objective prevention of destruction or loss of function of the kidney on the affected side. Maintenance of urinary flow is aided by the irregular shape of most ureteral calculi. Repeatedly, we have seen linear grooves and irregular channeling in the presence of hopelessly impacted stones that have been present for years with no apparent renal damage.

However, clinical evidence of renal back pressure confirmed by intravenous urograms indicating complete ureteral obstruction or a progressively enlarging hydronephrosis signifies that conservative methods of treatment are unwarranted, and surgical intervention should be carried out.

Dourmashkin[11] states that the important thing to remember in cases of advanced chronic infection is that the kidney is left with but a narrow margin of the remarkable tendency to speedy recovery exhibited by a kidney which becomes acutely infected in the course of sudden ureteral block of recent origin. To subject such patients to prolonged cystoscopic treatment may only result in losing the small chance of bringing about renal recovery.

(4) *General Health of the Patient:* Elderly, debilitated men may not tolerate instrumental manipulations well, and severe clinical reactions may result. Some patients are more susceptible to febrile reactions following manipulative procedures, and once a severe febrile reaction has occurred, further instrumentation must be considered hazardous.

Moore[12] states that if infection is acute, severe, and characterized by repeated rigors, hyperpyrexia, and leukocytosis in the presence of an obstructing calculus, prompt surgical interference, with establishment of free drainage, may become a life-saving measure.

However, in order to prepare a ureteral calculus patient for operation we have at times used an indwelling ureteral catheter, which is of inestimable value in bringing about the quiescence of a septic course.

In elderly patients, associated pathology, such as prostatic hypertrophy, makes manipulative procedures technically difficult and febrile reactions more likely to occur. In such cases, operation may be the procedure of choice. To use more conservative methods may produce prolonged sepsis, which, in turn, may result in precipitation of cardiorenal failure.

In small children, due to technical difficulties, inability to secure good coöperation, and the necessity of repeated anesthesia, I believe open operation is the procedure of choice.

Transurethral Manipulations.—In our experience the use of single and multiple catheters has been most successful, with minimal complications. There is some difference of opinion regarding the value of mechanical stone removers. We agree with Coppridge,[13] who believes their use should be restricted to

stones in the lower third of the ureter (Fig. 2). Although it requires more patience on the part of the surgeon and the patient, it is usually safer to continue with repeated manipulations and dilatations with catheters than to attempt forcibly to remove the stone by any method employing traction.

Recent reports in the literature reëmphasize to us the importance of conservative procedures. Perforation of the ureter has been reported by Councill,[14] Rusche and Bacon,[15] and Vickery.[16] Wishard[17] has reported a case of incarceration of a stone basket in the ureter due to a broken wire.

The large number of instruments available today for the removal of stones in the ureter attest to the fact that no one instrument or method is suitable in all instances.

Our current treatment of upper and midureteral stones is, in the absence of complications, a policy of watchful waiting. If the calculus is 1 cm. in diameter, or less, and is moving spontaneously down the ureter, manipulative treatment is delayed until the stone reaches the pelvic portion. Then the use of multiple catheters or a basket extractor is advised. If the stone in the upper or midureter is producing complete obstruction, as evidenced by intravenous urography, then surgical intervention is advocated.

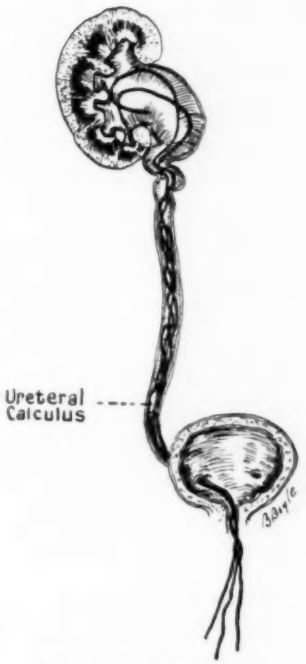


FIG. 2.—Multiple ureteral catheters for the removal of stones in the lower ureter.

Calculi in the intramural segment of the ureter present a characteristic picture on cystoscopic examination. There is a bulging immediately above the ureteral orifice and an area of bullous edema about the orifice itself. In this group a meatotomy can be performed and the stone withdrawn by use of the spiral extractor.

If the intravenous urogram demonstrates considerable dilatation of the ureter above the calculus, only a meatotomy is performed, and manipulation is avoided. In such instances manipulation may result in dislodging the stone, which may slip up to the kidney pelvis. Prostigmine is used for a period of 24 hours to aid in the expulsion of the stone.

Although we are very enthusiastic regarding manipulative management of ureteral calculi, it is our impression that this method may be advocated too extensively, and that it is frequently employed in cases where surgical intervention would lessen the hardship on the patient and be attended with a lower mortality and morbidity.

Operative treatment.—Spinal anesthesia is the anesthesia of choice for the surgical removal of stones from the ureter. Immediately before operation it is advisable to check the location of the calculus roentgenographically. This is a

fundamental rule, but too frequently it is omitted and the surgeon finds that the stone has slipped into the bladder or back into the kidney during the night before operation. Such errors of omission are inexcusable and subject the patient to needless loss of time and hazards of operation.

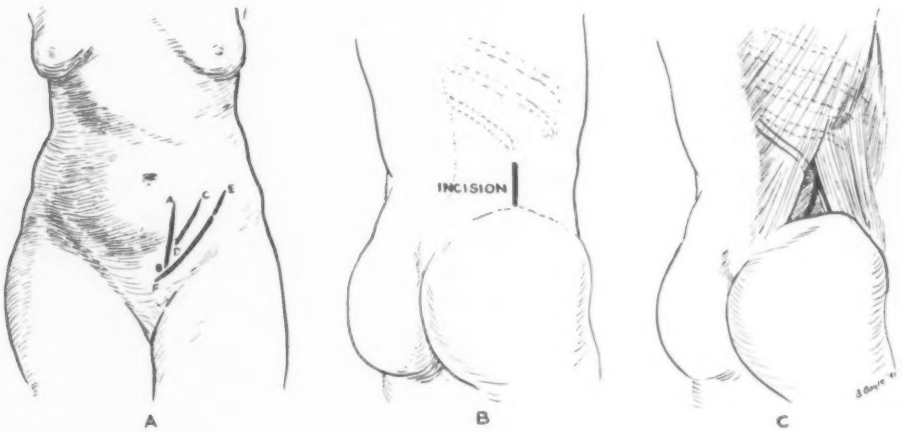


FIG. 3.—Incisions for removal of calculi in various portions of ureter. (A) Stones in lower ureter; (B) stones in midureter; (C) stones in upper ureter.

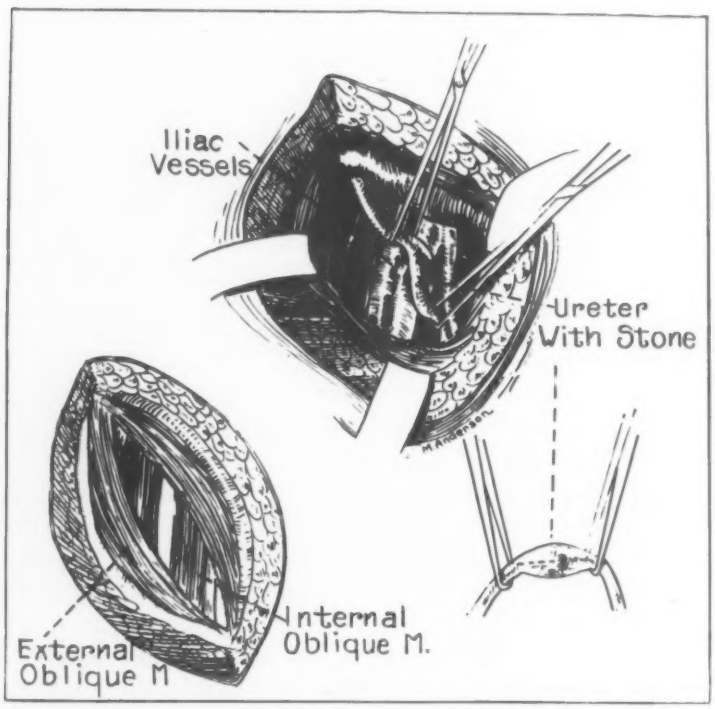


FIG. 4.—Technic for removal of calculus in lower ureter.

A muscle-splitting operation and extraperitoneal approach are utilized in removing stones from every point of the ureter (Figs. 3, 4, 5). The type of approach reduces pulmonary and circulatory complications, in view of the fact that patients are ambulant in five or six days. Incisional herniae are also reduced by this procedure.

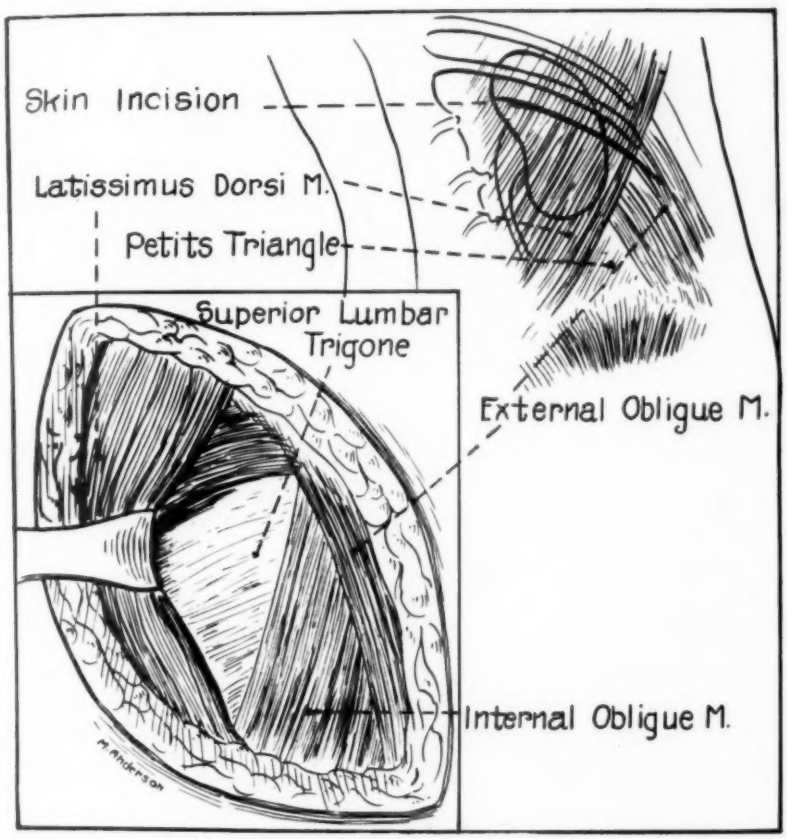


FIG. 5.—Incision for removal of stone in mid and upper ureter.

There is one operative procedure for the removal of a stone from the lower ureter that has received but scant attention. This is vaginal ureterolithotomy. If the calculus can be palpated upon vaginal examination it may be readily removed by this route (Figs. 6, 7, 8). We have observed no fistula formations, or other complications, following this surgical procedure.

Complications must be considered when methods of removing calculi are carried out. The choice between radical and conservative treatment of the hydronephrotic kidney is influenced upon the extent of renal function impairment and the status of the other kidney. A draining ureteral fistula, or a pyonephrotic kidney may make nephrectomy or nephroureterectomy imperative. However, many kidneys with varying degrees of hydronephrosis will

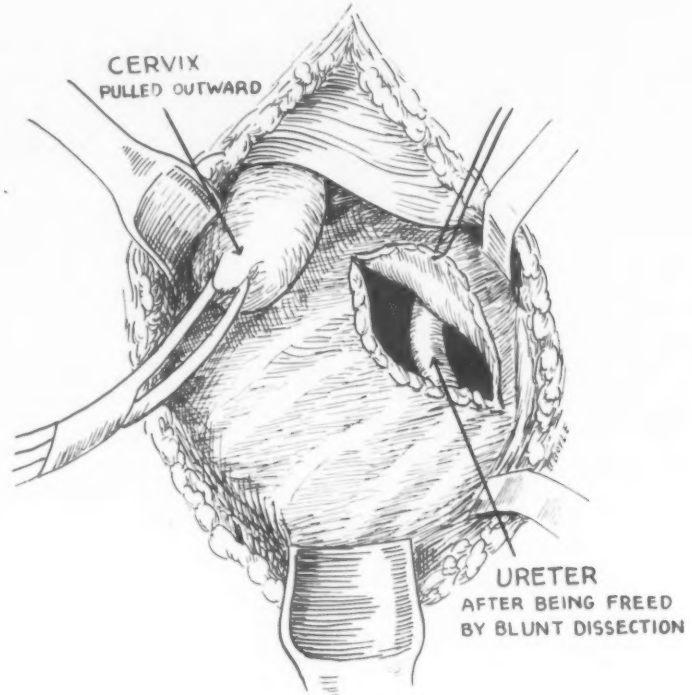


FIG. 6.—Vagino-ureteral lithotomy with exposure of ureter.

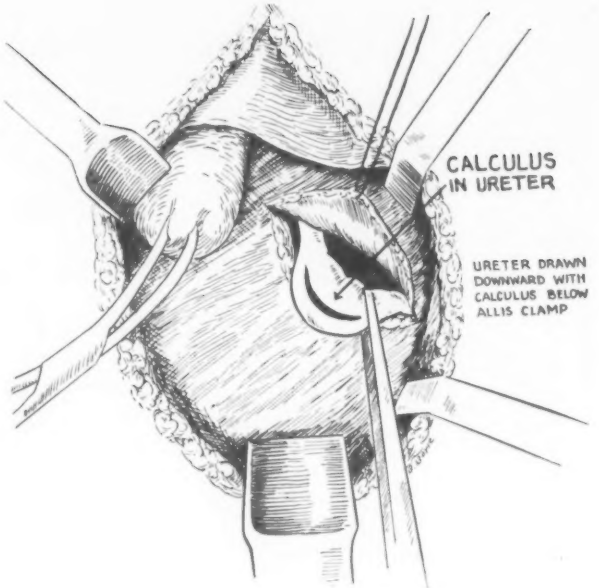


FIG. 7.—Removal of calculus from ureter.

return to an amazingly good state when the obstruction is removed and drainage established.

Certainly, dogmatic statements specifying indications are unwarranted, but in our experience operation has been resorted to for the following reasons: (1) repeated failure of manipulative methods; (2) impassible obstructions due to stones that cannot be moved; (3) renal infections which endanger the life of the patient by temporization; (4) associated pathology which makes instru-

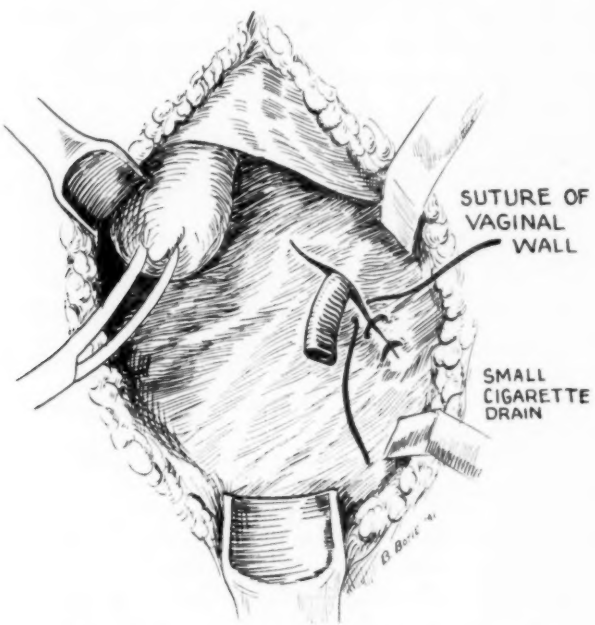


FIG. 8.—Closure of incision in vaginal wall.

mental attempts technically impossible (urethral strictures, hypertrophy of prostate, *etc.*); (5) upper urinary tract pathology, which itself requires surgery; and (6) patients who cannot tolerate transurethral manipulation.

During the past decade three series of ureteral stone cases have been reported at Cleveland Clinic (Table IV).

TABLE IV

COMPARISON OF FINDINGS IN THREE SERIES OF CASES

Series	Cases	Spontaneous Expulsion %	Expelled after Manipulation	Surgical Interference
1-1939[1]	251	43-17.1%	37-14.7%	171-68.4%
2-1942	350	66-18.9%	56-16%	228-65.1%
3-1946	256	29-11.3%	149-58%	78-30%

CONCLUSIONS

1. Investigation of the numerous etiologic factors in each ureteral stone case is important.

2. The plan of management for each case must be individualized.

3. In our experience ureteral catheter manipulations are superior to mechanical stone extractors, although the latter are a valuable adjunct in many instances.

4. The current trend at Cleveland Clinic in the treatment of ureteral calculi is definitely toward conservative management by manipulation rather than by open surgery.

REFERENCES

1 Mathe, C. P.: Diagnosis and Present-day Treatment of Ureteral Stone. J. Urol., **28**, 133–155, August, 1932.

2 Ravich, A.: Critical Study of Ureteral Calculi: Based on Series of 758 Private Cases. J. Urol., **29**, 171–185, 1933.

3 Bumpus, H. C., Jr., and Scholl, A. J.: Ureteral Stones. S. Clinic N. America, **5**, 813–827, June, 1925.

4 Higgins, C. C.: Ureteral Calculi: Review of 350 Cases. Nebraska M. J., **27**, 301–308, September, 1942.

5 Kretschmer, H. L.: Stone in Ureter: Clinical Data Based on 500 Cases. Surg., Gynec., and Obst., **74**, 1065–1077, June, 1942.

6 Bumpus, H. C., and Thompson, G. J.: Stones in the Ureter. Surg., Gynec., and Obst., **50**, 106–109, 1930.

7 Carp, I. J.: Ureteral Calculus: Analysis of 100 Cases. Urol. and Cutan. Rev., **41**, 587–589, August, 1937.

8 Peterson, H. O., and Holmes, G. W.: Roentgen Analysis of 100 Cases of Ureteral Stone. Am. J. Roentgenol., **37**, 479–483, April, 1937.

9 Joly, J. S.: Stone and Calculous Disease of the Urinary Organs. St. Louis: C. R. Mosby, 1931.

10 Thompson, G. J., and Kibler, J. M.: Treatment of Ureteral Calculus: With Particular Reference to Transureteral Manipulation. J. A. M. A., **114**, 6–12, January 6, 1940.

11 Dourmashkin, R. L.: Cystoscopic Treatment of Stones in Ureter: With Special Reference to Large Calculi: Based on a Study of 1,550 Cases. J. Urol., **54**, 245–283, September, 1945.

12 Moore, T. D.: Factors Determining Management of Ureteral Stones: Improved Method of their Cystoscopic Removal. J. Urol., **37**, 1–11, January, 1937.

13 Coppridge, W. M.: Clinical Management of Ureteral Stones. South. M. J., **33**, 18–21, January, 1940.

14 Councill, W. A.: Treatment of Ureteral Calculi: Report of 504 Cases in Which Councill Stone Extractor and Dilator Was Used. J. Urol., **53**, 534–538, April, 1945.

15 Rusche, C. F., and Bacon, S. K.: Injury of Ureter Due to Cystoscopic Intraureteral Instrumentation: Report of 16 Cases. J. Urol., **44**, 777–793, December, 1940.

16 Vickery, E. P.: Urologists' Letters. P. 83, 1936.

17 Wishard, W. N.: Stone in Lower Third Ureter: With Report of an Instance of Incarcerated Basket. J. Urol., **50**, 775–783, December, 1943.

18 Engel, W. J.: Management of Stone in Ureter. S. Clin. North America, **19**, 1275–1284, October, 1939.

Cleveland Clinic
Euclid Ave. at 93rd St.
Cleveland 6, Ohio

CAROTID BODY TUMORS*

WILLIAM S. MACCOMB, M.D.
NEW YORK, N. Y.

FROM THE HEAD AND NECK SERVICE, MEMORIAL HOSPITAL, NEW YORK CITY, N. Y.

CAROTID BODY TUMORS rarely are seen on the surgical services of most hospitals. In 1935, Peterson & Meeker[1] presented before the New York Surgical Society a series of 18 such tumors, collected from seven hospitals of New York City. At that time, none were listed from Memorial Hospital. Since 1937, ten patients have been treated for carotid body tumors, on the Head and Neck Service of this Institution.

The first report of a tumor of carotid body origin to appear in the American literature was that by Scudder,[2] in 1903. Since then a survey of the literature shows an accumulation of nearly 300 tumors of this type. Many single case reports have been listed. The largest individual series has been that from the Mayo Clinic, published in 1941, by Harrington, Clagett and Dockerty.[3] Twelve patients of their series of 20 had been reported previously by Rankin and Wellbrock.[4]

As the anatomy and histology of the carotid body have been described frequently they will not be discussed at this time.

Embryology.—There is no unanimity of opinion as to the developmental anatomy of the carotid body. Theories of origin are that it arises from (1) the epithelium of the pharynx; (2) the endothelium or adventitia of the carotid artery; and (3) the embryonic ganglion cells of the sympathetics.

Function.—The exact function of the carotid body still has not been established definitely. For many years there was believed to be an internal secretion from this gland. The chromaffin granules of the carotid body were considered as at least precursors of epinephrine, but this theory now has been disproved. In the human, the carotid body can be found in not more than 25 per cent of autopsy specimens.

An article on the functions of the carotid and aortic bodies from the Department of Pharmacology of the University of Pennsylvania was published in 1940. The authors, Schmidt and Comroe,[5] have made extensive investigations of the functions of the carotid body in the dog. They conclude that the major function of the carotid body, and probably of the aortic bodies, is due to the presence within them of chemoreceptors which respond to chemical changes in the blood.

Reflex receptors in the carotid body seem to be specialized to respond to changes in the oxygen tension of the blood, whereas cells of the respiratory center respond to changes in the carbondioxide tension. The hydrogen ion may be an important factor in regulating chemoreceptor activity. Schmidt and Comroe's[5] experiments indicate that "the activity of the receptors can be

* Read before the New York Surgical Society, April 10, 1946.

altered by a variety of chemical agents including all the usual products of tissue metabolism. . . ." Recent workers agree that carotid bodies and aortic bodies are not "chromaffin" in the usual sense, which is further evidence that they may not be related to the sympathetic nervous system. According to the Mayo Clinic report of 1941,[3] "the carotid body is no longer considered part of the internal secretory system and the function whatever it may be, is negligible since both carotid bodies can be enucleated without any manifest symptoms."

Pathology.—Most carotid body tumors appear to be benign in nature, yet some authors have stated that as many as 50 per cent are malignant. Although eight of the 18 tumors of the series from New York Hospitals had been diagnosed as malignant, Peterson and Meeker[1] considered their malignant status to be uncertain. In the Mayo Clinic Series ten of the 20 tumors were found on microscopic examination to be malignant. In the Memorial Hospital Series of ten patients, five tumors were reported to be malignant and five were benign. In the case of bilateral tumor, both were malignant.

Microscopically, the benign tumors are found to be extremely vascular. Small cells predominate in a uniform pattern and fibrosis is less pronounced. In the more malignant group pleomorphism occurs. The cells contain small nuclei. Invasion of the capsule and of lymphatics is found. A few tumors of this group are extremely fibrotic in character.

Incidence.—Carotid body tumors occur most frequently in the third and fourth decades of life, with no predominance in either sex. The present series of ten patients is composed of seven males, the youngest being 24 years of age, the oldest 57 years; and three females, the youngest 20 years of age and the oldest 31 years. The average age for the entire group is 36 years. In this group six had tumors on the left side; three on the right side; and one was bilateral.

Symptomatology.—The usual complaint of the patient suffering from a carotid body tumor is the presence of a "mass" or "lump" in the neck. Frequently it has been found that the tumor had been observed first some years before and that the patient came for treatment because he believed the mass had increased in size. This was the only symptom in six patients of the present series. In three patients, however, the presence of a pharyngeal mass was the chief complaint. Although a similar enlargement was found on examination of a fourth patient he was not aware of its presence. The average duration of the presence of the tumor in the neck for this group was five years. On admission, two patients were found to have a Horner's syndrome and two had paralysis of a vocal cord. Another patient of the group associated systemic symptoms of malaise, mild headaches, depression and occasional febrile reactions with the increasing size of the neck tumor, but it seems unlikely that these attacks were caused by the tumor itself.

Diagnosis.—Gordon-Taylor[6] has said that carotid body tumors are rarest of all tumors in the neck. In the period of nine years, when the present series of ten carotid body tumors was being accumulated, an average of 1,200 new patients were examined in the Head and Neck Department of Memorial Hospital. The possibility of an unexplained cervical growth being a carotid body

tumor is evidently small. However, in the present series, four correct clinical diagnoses were made. In three of the four, the diagnoses were confirmed pathologically by aspiration biopsy. In the remaining six patients of the series, aspiration biopsy was performed, but it was impossible to obtain sufficient tissue for diagnosis. The first patient with a carotid body tumor was admitted to the clinic in 1937. An aspiration biopsy was performed and an erroneous diagnosis of "carcinoma, possibly thyroid" was made. However, when the second patient in the series appeared, a clinical diagnosis of carotid body tumor was made and confirmed by pathologic examination. It has been stated by some authors that aspirating such a vascular tumor would be an extremely hazardous procedure but this supposition has not been proven at Memorial Hospital.

TREATMENT

Most authors agree that carotid body tumors should be removed surgically. Yet, the necessity of ligation of the common and internal carotid arteries occurs so frequently that because of the high postoperative mortality it might be better to refrain from this procedure, were it possible to be certain of the benign nature of the tumor. The possibility of a benign tumor later becoming malignant must be kept in mind however. Goodof and Lischer[7] have published an article describing a carotid body tumor in a 47-year-old Negro. The cervical growth measured six centimeters in diameter. The blood Wassermann was positive, and antiluetic therapy was instituted. After two months of treatment the patient failed to return. Fifteen years later he was readmitted to the same institution in cardiac failure. The cervical tumor had grown to twice the size of that recorded on the first examination. At autopsy, a tumor, similar in character to the carotid body tumor was found in the pancreas. Mitotic figures were present in both tumors. The authors considered the neoplasms to be multicentric in origin. The cause of death was unrelated to the presence of either tumor.

Mortality rates for surgical excision of carotid body tumors, with ligation of the common and internal carotid arteries, are reported from 0 to 100 per cent. Such results demand careful consideration before an operation is undertaken which may require resection of the carotid arteries. Postoperative disabilities are estimated to be as high as 83 per cent. They consist of temporary or permanent hemiplegia and the effects of injuries to the cervical sympathetic, hypoglossal or vagus nerves.

In the present series of ten patients the carotid body tumor was resected without injury to the arteries in only three instances. In the other seven patients it was necessary to include the carotid arteries in the resection of the tumor. There were four postoperative deaths, occurring in 30 hours, two days, five and five days, respectively. Hemiplegia preceded death in each instance. In one patient ligation of the common carotid caused a convulsion, followed by hemiplegia on the operating table, although a Matas' band had been applied for compression of the common carotid three days before the major operation

was performed. In this case, it seems likely that cerebral anemia caused the convulsion and hemiplegia, though the patient was only 31 years of age. The postoperative mortality rate for the seven patients requiring removal of the carotid arteries is 58 per cent. Of the total group of ten it is 40 per cent.

Recurrence of the tumor takes place in about seven per cent of the patients, according to Phelps and Snyder.[8] Recurrences are possible when the capsule is invaded or the entire tumor is not removed. The latter condition may be the result of attempting to dissect a closely adherent tumor from the arterial wall. One tumor of the present series recurred and was again removed surgically. The patient died at home with extensive recurrences in the cervical region, but unfortunately an autopsy could not be obtained.

Fatalities following carotid ligations are usually the result of insufficient collateral cerebral circulation or an ascending thrombosis in the internal carotid artery.

External compression of the common carotid artery, as described by Matas,[9] is undoubtedly of value in testing for the efficiency of the collateral cerebral circulation. Dandy[10] has emphasized the fact that if a patient cannot withstand the Matas test an immediate total occlusion of the carotid artery should not be done.

The use of increasing periods of daily external compression may be of some aid in improving the compensatory flow of blood through the circle of Willis but some authors question the value of this procedure.

Dandy[10] has stated that "a high percentage of patients, regardless of age (but certainly increasing with age) will not tolerate total ligation of the carotid, but by partial closure of the carotid the cerebral collateral circulation becomes quickly established, and complete closure can be safely concluded later." He advocates the use of a double strip of fascia lata to attain partial closure of the common carotid artery.

An ascending thrombosis in the internal carotid artery theoretically is caused by the trauma to the intimal wall by the application of the ligature. This injury may be prevented by the interposition of a strip of fascia lata between the ligature and the wall of the artery, as advised by Dandy.

Heparin has been used in four patients on the Head and Neck Service following ligation of the carotid arteries during the removal of the metastatic cancer. No fatalities have resulted. There was one disability which consisted of temporary partial paralysis of an upper extremity. In this patient fascia lata had also been used in ligation of the internal carotid. Heparin was used also in three instances of this series of carotid body tumors. In one patient there were no postoperative complications. In the other two patients hemiplegia had already developed before the heparin was administered, and, therefore, the drug was ineffective.

CASE REPORTS

Case 1.—W. M., a 47-year-old white male, was admitted to the Clinic, in June, 1937, and had been aware of a "lump" in the left neck for ten years. It had been increasing in size for the last three years. Examination revealed an 8-cm., smooth ovoid mass over the left carotid bulb. The patient also had a constriction of the left pupil.

Tissue was obtained for pathologic examination on the second aspiration. It was diagnosed as carcinoma—possibly of thyroid origin.

In view of the pathologic report, a course of roentgenotherapy was started. After two-thirds of the treatments were administered without regression of the tumor, roentgenotherapy was abandoned in favor of surgery.

Operation was performed August 27, 1937, under local anesthesia. The tumor, at operation, could not be dissected free of the carotid arteries. The common carotid was compressed for 20 minutes without apparent ill effect. Then all three carotids were ligated and removed with the tumor. The hypoglossal and superior laryngeal nerves were sacrificed.

There were no postoperative complications. The Horner's syndrome persisted. The 9th, 10th, and 12th cranial nerves showed evidence of paralysis.

The pathologic report was carotid body tumor. No malignant changes were noted.

Case 2.—A. P., a 24-year-old white male, was admitted to the Clinic, January, 1940, and had had a "lump" in the left neck for two years, and associated systemic symptoms of malaise, headache, depression and occasional febrile reactions, with the increasing size of the tumor. Examination revealed a 5-cm. ovoid mass beneath the angle of the right lower jaw. The clinical diagnosis was Hodgkin's disease or carotid body tumor.

Sufficient tissue for pathologic examination was obtained on the third aspiration. It was reported as carotid body tumor.

At operation, January 28, 1940, under local anesthesia, an intricate plexus of blood vessels was found covering the tumor mass, and the common carotid artery, and extended over the sternomastoid muscle and the strap muscles of the neck. A Crile clamp was placed on the common carotid artery. After 15 minutes ligation was completed. The sympathetic cervical chain was sacrificed.

The postoperative course was uneventful. A Horner's syndrome was the only abnormality noted.

Pathologic study revealed carotid body tumor, with malignant changes. Eleven months after operation the patient returned with a node at the operative site. He did not return for another six months. At that time, the mass measured 5 cm., and presented in the pharyngeal space. Aspiration biopsy suggested recurrence.

Second operation—October 9, 1941: The second operation was done under sodium pentothal. The mass was intimately associated with the wall of the esophagus and extended to the level of the first cervical vertebra. Eight gold seeds (11 mc.) were placed at this level. Pathology reported the growth as recurrent carotid body tumor, with vein and node invasion.

There were no immediate postoperative difficulties. Six months later, many large nodes were found in either side of the neck. The patient complained of headache, double vision, and generalized symptoms. The 6th cranial nerve was involved, and it seemed likely that the disease had entered the base of the skull. The patient died at home a year after the second operation; two years after the first. No autopsy could be obtained.

Case 3.—A. D., a 57-year-old white male, was admitted to Clinic in November, 1940. He complained of a mass in the left neck of 14 years' duration, which had recently become tender. Examination revealed a smooth ovoid mass of 5 cm. over the carotid bulb. Aspiration biopsy was negative. A clinical diagnosis of branchiogenic cyst was made. Three more attempts were made unsuccessfully to obtain diagnostic tissue by aspiration. Clinical diagnosis of carotid body tumor was made at this time.

Operation was performed under local anesthesia, November 22, 1940. The tumor was removed without ligation of the carotid arteries or sectioning of nerves.

The pathologic report was carotid body tumor, without evidence of malignant change.

Case 4.—M. B., a 44-year-old white male, was admitted, July, 1940, complaining of a "swelling" in the left neck of six months' duration. Examination revealed a smooth ovoid

mass of 4.5 cm. over the left carotid. It had the consistency of a metastatic node. Because the left tonsil was enlarged and firm, the patient was advised to enter the hospital to have it removed for biopsy. This the patient refused to do.

It was six months before he returned. At that time, because of the slow growth of the tumor, a diagnosis of carotid body tumor was considered. The original aspiration biopsy was reviewed and the diagnosis of carotid body origin was considered possible. A second aspiration at this time gave a more typical picture of a carotid body tumor.

Operation was performed, under local anesthesia, in July, 1941. A Crile clamp was applied gradually over a period of eight minutes, without any ill effects. All three carotids were ligated and removed with the tumor. The patient's immediate postoperative condition seemed good, but he never regained complete consciousness, and developed hemiplegia within 12 hours. He died on the 5th postoperative day.

The pathologic report was carotid body tumor, with malignant changes.

Case 5.—A. C., a 31-year-old white male, was admitted to Clinic in February, 1942. He complained of a mass of the left neck of three years' duration. Examination revealed a firm mass of 6 cm. in the left upper neck. The left pharyngeal wall presented a non-ulcerating, bulging mass extending from the nasopharynx to the tip of the epiglottis. Both masses seemed to be a part of the same tumor. A provisional diagnosis of carotid body tumor was made, and confirmed by aspiration.

Operation.—March 30, 1942: Under local anesthesia, the common carotid artery was compressed by a Matas band. This operation was preceded by three days of intravenous sodium thiosulfate (1 gm. in 10 cc. daily). No symptoms resulted from the carotid compression.

Four days later, April 3, 1942, the tumor was removed. The procedure was carried out under local anesthesia. The common, external and internal carotid arteries were ligated and the vagus and hypoglossal nerves cut. Fifteen minutes after the carotid was sectioned, the patient had a convulsion, and a complete right-sided paralysis developed. There was no thrombus in the common carotid at this time. Hemiplegia was probably due to incomplete blood supply to the brain. The patient died 48 hours postoperatively.

Pathologic report on the operative specimen was carotid body tumor, with no suggestion of malignant change. Permission for autopsy could not be obtained.

Case 6.—F. S., a 31-year-old white female, was admitted to the hospital, in April, 1942. She had been referred by her local physician for removal of a tumor beneath the right lower jaw. Examination revealed a firm ovoid node, about 2.5 to 3 cm. in size. Aspiration biopsy was attempted but no tissue was obtained.

The tumor was removed under local anesthesia, April 24, 1942. A great deal of fibrous tissue surrounded the mass. In dissecting around the carotid bulb the thinned-out artery wall was irreparably damaged. A sponge clamp applied to the common carotid artery early in the operation had been in place 45 minutes when the hemorrhage occurred. There were no circulatory disturbances. All carotid arteries were ligated.

There were no postoperative difficulties until 36 hours after operation, when the patient developed a right hemiplegia. Heparin had not been administered until the paralysis developed. The patient died on the 5th postoperative day. Permission for autopsy was not obtained.

The pathologic report was carotid body tumor. It was benign.

Case 7.—M. V., a 29-year-old white male, was admitted to the Clinic, in July, 1943. He complained of a "swelling" in the left neck of one year's duration. He had previously been treated in another hospital for tuberculous osteomyelitis. Examination revealed a node, 3 cm. in diameter, in the left submaxillary region and a smaller node anterior to it. The provisional diagnosis was tuberculous adenitis.

The tumor was removed, August 8, 1943, under local anesthesia, without ligation of the carotids or sectioning of nerves.

There were no postoperative complications. The patient was free of disease when last seen.

The pathologic report was carotid body tumor. It was benign.

Case 8.—J. D. V., a 20-year-old white female, was referred to the hospital from a local clinic, in September, 1944. She had noticed a small "lump" beneath the angle of the left lower jaw a year and one-half previously. A biopsy had been taken from the nasopharynx and reported as transitional cell epithelioma, Grade 2. A few roentgen ray treatments had been administered before she was referred to Memorial Hospital.

Examination revealed a bulging, nonulcerating mass of 4 cm. in the posterolateral pharyngeal wall, which seemed a part of the mass present in the right neck. The patient had a right Horner's syndrome. The nasopharyngeal biopsy from the local clinic was reviewed by the Pathology Department, but the diagnosis of epithelioma could not be confirmed. Two attempts to obtain tissue by aspiration were unsuccessful.

Operation was performed, September 25, 1944, under sodium pentothal. A tracheostomy was established first. The tumor, measuring 6 cm., was removed. The vagus and hypoglossal nerves were sacrificed. The tumor was dissected free of the carotid arteries. Aside from signs of vagus and hypoglossal paralysis, there were no postoperative sequelae.

The pathologic findings were carotid body tumor and lymph node, showing metastasis or extension. The tumor was malignant in character. She recently reports improvement in difficulty in swallowing. There has been no recurrence of the disease.

Case 9.—A. T., a 20-year-old white female, was admitted to the Clinic, in June, 1943, for a "lump" in the right neck of two years' duration. Biopsies of the tonsil and the neck node had been made at another hospital. A telephone report of hyperplastic lymphoma of the tonsil was received, but no report concerning the neck node could be obtained. Examination revealed a mass, 5 cm. x 2.5 cm., in the right tonsillar fossa. The right vocal cord was paralyzed and the right arytenoid edematous. A large subdigastric node, 4 cm. x 3 cm., was present on the right side. Other smaller nodes were present on both sides of the neck. A provisional diagnosis of lymphosarcoma was made. Chest roentgenograms and blood studies were normal. The Kline test was three plus.

Attempts at aspiration and open biopsy of the neck node yielded no diagnostic tissue.

For several months the patient received treatment for lues and active gonorrhea at another hospital.

Operation was performed, March 19, 1945, under sodium pentothal, with a tracheostomy tube in place. The vabus and hypoglossal nerves were sacrificed. The carotids were sectioned. The mandible was sectioned obliquely at the angle to permit extending the operation into the pterygomaxillary space.

Heparinization was begun postoperatively and was maintained for three days. No hemiplegia developed. Hoarseness continued. The patient had considerable difficulty in swallowing.

The pathologic findings were carotid body tumor, with marked fibrosis and malignant changes. There has been no recurrence of the disease to date.

Case 10.—E. B., a 52-year-old male, was admitted to the Clinic with a mass in the right neck which had been noted first 13 years previously. It had been treated by local physicians, first, as an abscess by excision, which caused profuse bleeding, then, as tuberculous adenitis by roentgenotherapy. In May, 1945, he was referred to Memorial Hospital. Examination showed a 6-cm. tumor in the right lateral pharyngeal wall. It pulsated on palpation. A 3-cm. mass was present in the region of the right carotid bulb. A similar mass was present over the left carotid bulb. There was paralysis of the right side of the larynx. Only blood was obtained on aspiration. The clinical impression was schwannoma.

Operation was performed under local anesthesia, July 15, 1945. It was necessary to ligate the carotids and sever the vagus. Following this procedure the blood pressure

dropped and respirations ceased. Artificial respiration was administered. The patient was returned to the ward in poor condition, and was placed in an oxygen tent. There was evidence of left-sided hemiplegia immediately following operation. Heparin was administered postoperatively. On the evening of the day of the operation paralysis developed on the opposite side. He expired 30 hours postoperatively.

The pathologic findings from the operative and autopsy specimens were bilateral carotid body tumor, with structure in places malignant in each of the tumors.

TABLE I

SUMMARY OF MEMORIAL HOSPITAL SERIES OF CAROTID BODY TUMORS

1937–1945

I. Incidence:	
A. Number of patients	10
1. Male	7
2. Female	3
B. Average of patients	36 years
1. Oldest	57 years
2. Youngest	20 years
II. Distribution:	
A. Right-sided	3
B. Left-sided	6
C. Bilateral	1
D. Recurrent	1
III. Symptoms:	
A. Cervical tumor	6
B. Cervical and pharyngeal tumor	4
C. Nerve involvement:	
1. Vagus	3
2. Cervical sympathetic chain	2
3. Hypoglossal	0
IV. Diagnosis:	
A. Correct preoperative—clinical	4
B. Correct preoperative—pathologic	3
V. Treatment:	
A. Preoperative roentgenotherapy before diagnosis of carotid body tumor	3
B. Surgical operation	10
1. Carotid arteries ligated	7
a. Total	7
b. Partial	1
2. Nerves were sectioned:	
(a) Vagus (2 right; 2 left)	4
(b) Cervical sympathetic chain	2
(c) Hypoglossal	4
VI. Pathology:	
A. Benign	5
B. Malignant	5
VII. End-results:	
A. Number living	5
B. Death from disease	1
C. Postoperative death (40%)	4
D. Rate of mortality following carotid resection	58%

CONCLUSIONS

Carotid body tumors are difficult to diagnose preoperatively. Aspiration biopsy offers a possibility of obtaining enough tissue to permit histologic diagnosis of carotid body tumor, although the pathologist usually is unable to determine from the small amount of tissue available, whether or not the tumor is malignant.

The high mortality of ligation of the common and internal carotid arteries is caused either by inadequate collateral cerebral circulation, or to an ascending thrombosis of the internal carotid artery. Hemiplegia occurs immediately in the former incidence, and in the latter 30 to 36 hours postoperatively.

If one could be certain that a carotid body tumor was benign in nature, it might be wise to keep the patient under observation and refrain from the use of surgery unless the increasing size of the tumor caused symptoms of pressure.

When a carotid body tumor is to be removed surgically, the patient should be hospitalized for a period of observation and preparation for operation. The Matas test should be utilized to determine collateral cerebral circulation and, if necessary, a partial occlusion should precede the total occlusion and removal of the tumor.

The use of heparin postoperatively is suggested as a possible means of preventing an ascending thrombosis in the internal carotid artery.

REFERENCES

1 Peterson, E. W., and Meeker, L. H.: Tumors of the Carotid Body. ANNALS OF SURGERY, **103**, 554, April, 1936.
2 Scudder, C. L.: Am. Jour. Medical Sc., **126**, 384, 1903.
3 Harrington, Stuart W., Clagett, O. T., and Dockerty, M. B.: Tumors of the Carotid Body. ANNALS OF SURGERY, **114**, 820, November, 1941.
4 Rankin, F. W., and Wellbrock, W. L. A.: Tumors of the Carotid Body. ANNALS OF SURGERY, **93**, 801, April, 1931.
5 Schmidt, C. F., and Comroe, J. H., Jr.: Functions of the Carotid and Aortic Bodies. Phys. Review, **20**, 115, 1940.
6 Gordon-Taylor, Gordon: Carotid Gland Tumors. Brit. Jour. of Surg., **28**, 163, October, 1940.
7 Goodof, Irving, and Lischer, Carl E.: Carotid Body Tumor and Similar Lesion in Pancreas. Arch. Path., **35**, 906, June, 1943.
8 Phelps, F. W., and Snyder, G. A. C.: West. Jour. Surg., **45**, 42, 1937.
9 Matas, R.: Testing the Efficiency of the Collateral Circulation as a Preliminary to the Occlusion of the Great Surgical Arteries. J. A. M. A., **63**, 1441, October 24, 1914.
10 Dandy, Walter E.: Results Following Ligation of the Internal Carotid Artery. Arch. of Surg., **45**, 521, 1942.

962 Park Avenue
New York 28, N. Y.

MESENCHYMOMA, THE MIXED TUMOR OF MESENCHYMAL DERIVATIVES*

ARTHUR PURDY STOUT, M.D.
NEW YORK, N. Y.

MOST OF THE TUMORS which presumably are formed from the cellular derivatives of the mesenchyme assume a guise which should enable one to recognize their nature microscopically and to label them with a properly descriptive name. It is important that this be done, for the different types of tumors are affected by irradiation in varying degrees and pursue biologic courses which differ one from the other so that the treatment best designed to produce favorable results is not the same in every case. During the past 75 years knowledge concerning those tumors, which are composed of cell masses more or less resembling the various derivatives of the supportive and reticuloendothelial tissues, has slowly accumulated and criteria now exist for recognizing malignant neoplasms composed of lipoblasts, synovioblasts, rhabdomyoblasts, and several others, and the terms liposarcoma, synovial sarcoma, rhabdomyosarcoma, etc., can be used instead of such vague and inaccurate names as spindle-, round-, and giant cell sarcoma. Correct labelling has permitted the accumulation of case histories of the tumors and there now exists a body of experience which serves as a guide to treatment.

Unfortunately these tumors of mesenchymal derivation do not always grow in a pure form. In the first place their cells may lose the special features which characterize them as formers of fat, muscle, synovial tissue, etc., and take on the function of making connective tissue fibers. In tumors like the synovial sarcoma such cells are always present and form an integral part of the tumor (Haagensen and Stout, 1944). In others, such as the liposarcoma, this feature is found in only a few of the neoplasms. In an occasional neoplasm, bone, cartilage, or both of them in differentiated form, may be found in the framework of the tumor as was the fact in Case 40 of the group of liposarcomas reported by the writer in 1944.

Another confusing situation arises when a preexisting lesion composed of heterotopic tissue suddenly develops a malignant neoplasm. The best example of this is the development of a sarcoma in an area of myositis ossificans. When this occurs, the differentiated bone and cartilage of the myositis ossificans may give rise to pure osteogenic or chondrosarcoma (Mallory 1933) or they may be intermingled with a malignant mesoblastic tumor of some unrelated type such as a reticulum cell sarcoma, as occurred in one of our cases. Since some atrophic or degenerate striated muscle fibers may also still be present, the resulting admixture of all these may provide a most confusing and complex histologic picture but because the bone and muscle are not neoplastic

* From the Surgical Pathology Laboratory, College of Physicians and Surgeons, Columbia University, and the Department of Surgery, Presbyterian Hospital, New York, N. Y.

and do not play an active rôle in the neoplasm, it cannot be considered as a true mixed tumor.

In addition to such vagaries of the growth of single cell tumors with metaplasia, there occur a variety of tumors in various parts of the body in which two or more tissue forms participate in the formation of both benign and malignant tumors. Many of those are composed of both epithelial elements as well as mesodermal derivatives such as the adenofibromas of the breast, the adenosarcomas of the kidney and the mixed tumors of mucous, salivary, lacrymal and sweat glands, to mention only three familiar types. There are also a variety of others which seem to be purely mesenchymal and it is upon these that attention will be focussed in order to emphasize the fact that they may be found in regions of the body not commonly associated with them.

Most of these mixed mesenchymal tumors probably are initiated as a result of developmental faults and they may therefore be regarded as dysontogenetic growths. In one tumor form capillaries, adipose tissue and smooth muscle are all present together. Such uncommon neoplasms are found usually in the muscles or subcutaneous tissues and either the blood vessels or the fat predominate with relatively small amounts of smooth muscle so that they are commonly labelled either hemangioma or lipoma (Stout, 1944). In a tumor of this sort described by Rocher and Uzac (1931) bone also was present. So far as my knowledge goes such tumors are always benign.

The benign hamartomas of the lung sometimes fail to contain any epithelial elements and are made up of differentiated bone, cartilage, fat and myxomatous tissue (McDonald et al. 1945). There are also the fibrous and fatty pedunculated tumors of the skin which vary from tiny pedunculated growths to neoplasms of huge proportions. These are usually called fibrolipomas or simply fibromas or lipomas depending upon which of the two tissues predominates. In the urogenital tract there are many benign mesodermal mixed tumors which are believed to be congenital. For example, there are benign mixed tumors formed in the kidney composed of mixtures of smooth muscle, fibrous and adipose tissue. These have been collected by Colvin (1942), who suggests for them the infelicitous name of capsuloma because most of them are attached to the deep surface of the capsule. Belonging in the same general category are the peculiar lipomas of the kidney capsule which contain areas of bone marrow in an active stage of hematopoiesis (Stout, 1932). Takács' (1942) uterine tumor which he called mesenchymoma embryonale angioplasticum, Gardner's (1940) fibromyoma angiomatosum, Limburg's (1942) lymphangiocystic fibroma of the uterus are all examples of the benign mesenchymal mixed tumor.

In addition to these benign forms, there are also a number of malignant tumors of the urogenital tract which are made up of a mixture of mesenchymal derivatives. Dreyfuss and Lubash in 1940 described what they called a malignant mixed tumor of fourteen years' duration and recent rapid growth attached to the spermatic cord. It was excised and recurred at once, leading to a second excision in two months. It was composed of both osteogenic sarcoma

and liposarcoma. Amolsch (1939), using the name mixed mesodermal tumor, described six cases of polypoid growths in the vagina and uterus of five adults and one child. One was not followed, one was symptom-free two years after the removal of a recurrence and the other four died of recurrences and metastases. These tumors were made up of myxoma, chondroblasts and rhabdomyoblasts. An example of a similar mixed mesodermal pedunculated tumor attached near the trigone of the bladder of an 83-year-old man has been recorded by Hirsch and Gasser (1944). It contained cartilage, osteoblastic tissue, myeloid cells and rhabdomyoblasts. The patient died five days after its removal. Other cases are referred to in their paper. The whole subject of the malignant mixed mesodermal tumors of the urogenital system has been comprehensively reviewed by McFarland (1935) who concludes that they can best be explained on the basis of dysontogenesis. Examples of similar growths in the female mammary gland without epithelial elements are discussed in the paper by Hill and Stout (1942). These cases have all been found in the urogenital tract and breast. One of the purposes of this paper is to emphasize the fact that malignant tumors of this variety are not confined to these tracts but have appeared elsewhere.

The cases of this sort to which attention is here directed are all potentially or actually malignant neoplasms composed of two or more cellular types any one of which, if taken by itself, might be considered a primary malignant neoplasm. It is unfortunate that proof of malignancy is lacking in all but three of these cases, yet knowing from experience the malignancy of the individual component parts of the other cases, it seems scarcely necessary to question their potential malignancy. As will be shown, every tumor differs from every other one in its cellular composition; they are alike only in the fact that all are actually or potentially malignant, all are mixed tumors compounded of cells and tissues of a variety ordinarily derived from primitive mesenchyme, not one of them can be fitted into the standard recognized varieties of sarcoma, and each one would have to receive a different compound name if they were to be designated by a term recording all of the component parts.

Table I shows the extraordinary breadth and variety of the tumor types found together in the eight cases. Almost all of the known varieties of malignant mesodermal neoplasms are represented with two cases showing five types —one showing four types, two having three types, and the rest two each. Perhaps one should not be too much surprised at these compounded growths. After all, the mesenchyme is an extremely versatile tissue, which in orderly development produces the normal prototypes of all of the tissues of which these malignant cells are the grotesque caricatures. It is surprising only, it seems to me, that there are not more tumors showing such admixtures. When one considers the performances of the tumoral derivatives of the neural crest which can reproduce in tumor form such mesenchymal tissues and cells as reticulin, striated muscle, fat, bone, cartilage and possibly kidney blastema, the productions of the mesenchymal cells seem the work of amateurs (Masson, 1938; Stout, 1946, 1947).

Some of the reports from the literature dealing with isolated cases of this sort show that the authors usually recognized their complex nature and had thoughts about their origin somewhat similar to those expressed above. Spéder and Lafforet (1937) described a huge tumor of the posterior surface of the thigh which weighed 11.9 kilos and was composed of areas of lipoma, osteoma, chondrosarcoma and osteogenic sarcoma. It metastasized to the mandible where it grew as a fibrosarcoma. They recorded the fact that M. E. Polosson in his Thèse de Lyon, 1925, proposed for similar giant tumors the name "conjontivome" which he stated had long been applied to branchiomas of the face and neck. Spéder and Lafforet emphasize that these tumors are characterized by long slow growth and a sudden change to malignancy. Gilmour's

TABLE I.—*Histopathologic Composition of Mesenchymomas*

Case	Sex	Age	Site	Composition										
				Fibrosarcoma	Myxoma	Liposarcoma	Leiomyosarcoma	Rhabdomyosarcoma	Osteogenic sarcoma	Chondrosarcoma	Reticulum cell sarcoma	Hemangioma	Hemangiopericytoma	Hemangioendothelioma
1	M	77	Gluteal muscles...	+		+	+		+					
2	M	45	Rectus fem. muscle				+		+	+	+	+		
3	M	70	Post. thigh muscles	+							+			
4	F	62	Uterus.....				+	+						
5	M	15	Lat. neck.....		+		+						+	
6	M	51	Pleura.....	+	+	+							+	+
7	F	35	Leg (subcutaneous)	+				+						
8	M	6	Liver.....		+	+						+		

(1943) patient had a tumor of the back which, during the course of 20 years, recurred locally six times and was apparently a liposarcoma showing erythroblastic activity. He suggested that it could be called a mesenchymoma. Another case which may possibly belong to this group is that of Rabson (1938) who, using the term "multiple mesenchymal hemendothelioma" described a 65-year-old man who died with multiple vascular neoplasms throughout the body.

In addition to blood vessels and primitive mesenchyme, bone and hematopoietic tissues were observed. The tumors at least demonstrated the potency of the mesenchyme to form tissues of differing types. The group of cases of extraskeletal ossifying tumors collected from the literature and from the Bone Sarcoma Registry of the American College of Surgeons by Wilson (1941) probably includes some malignant mesodermal mixed tumors, but it is impossible to be sure, for the bone was such a predominant feature that the other components of the tumors were referred to only as round and spindle cells

and their analysis not attempted. Case 8 in the present group has already been reported by Donovan and Santulli (1946). The authors got the name mesenchymoma from the pathologic report of Dr. Dorothy Anderson included in their paper. It was suggested to Dr. Anderson by the writer.

The names most favored by the authors of these papers are mesenchymoma or mesenchymal or mesodermal mixed tumor. Because the name mixed tumor has become so closely associated with the mixed tumors of the mucous, salivary, lacrymal and sweat glands and has also been used for other mixed tumors of the urogenital system and breast which contain epithelial structures, the writer feels that it is safer to use the word mesenchymoma to designate them. This word has had some fascination for other authors who, not realizing that it had already been preëmpted for use in describing malignant mesenchymal mixed tumors, have applied it to other growths. Thus Novak (1940) used it to describe the group of theca and granulosa cell tumors of the ovary and Tauber, Goldman and Bassett (1938) suggested it for what is probably an epithelioma of the skin.

CASE HISTORIES

Case 1.—N. M. (48362–50371), white male aged 77 years. Three weeks before admission a painless swelling appeared in the right buttock. On examination a deep mass measuring 10 x 7 cm. was found. 5/23/32 the mass was "shelled out" from its position deep to the gluteus maximus muscle and superficial to the fascia covering the pyriformis. 10/7/32 a local reappearance in the operative scar was removed with some of the surrounding muscle. This was ineffectual and 1/21/33 a third attempt removed a tumor 6 cm. in diameter from the region of the pyriformis and other external rotator muscles and the sciatic nerve. Postoperative radiotherapy did not check the persistent local extension of the tumor which continued until he died in a nursing home in September, 1934. It is unknown whether or not there were distant metastases. The original tumor and the first recurrence showed areas of fibrosarcoma and liposarcoma. The second recurrence showed a definite osteogenic sarcoma with areas of fibrosarcoma and probably leiomyosarcoma (Figs. 1 and 2).

Case 2.—W. S. (51071–75921), white unmarried English valet aged 45 years. He was first admitted to the Presbyterian Hospital 4/17/33 with a mass in the anterior region of the right thigh which had remained the size of a walnut for 4½ years but during the preceding six months had increased rapidly until it had reached dimensions of 14 x 10 x 5 cm. At operation the next day a fusiform knobby firm mass was found in the rectus femoris muscle near its junction with the tendon. It was removed with some of the surrounding muscle. Function was relatively good postoperatively because the crureus and vastus muscles compensated for the loss of the rectus. He remained well for more than five years when he developed cough and hemoptysis. Roentgenogram was suggestive of neoplastic lung involvement and he was treated with roentgenotherapy in the autumn of 1938. The disease progressed slowly and some doubt was felt about the nature of the process in the lung until 10/7/40, 7½ years after operation, when a bronchoscopic biopsy showed tumor. He then went steadily downhill as the tumor spread in his lungs in spite of a small amount of roentgenotherapy. He died 12/24/40, seven years and eight months after the tumor was first removed and over twelve years after its presence was first noted. The original tumor showed a growth made up of juxtaposed areas of osteogenic- and chondrosarcoma, reticulum cell sarcoma, leiomyosarcoma, and an angiomatoid proliferation of capillaries. The bronchus metastasis showed only the tumor reticulum cells (Figs. 3, 4, and 5).

FIG. 1.—Case 1: Mesenchyoma of deep gluteal muscles.

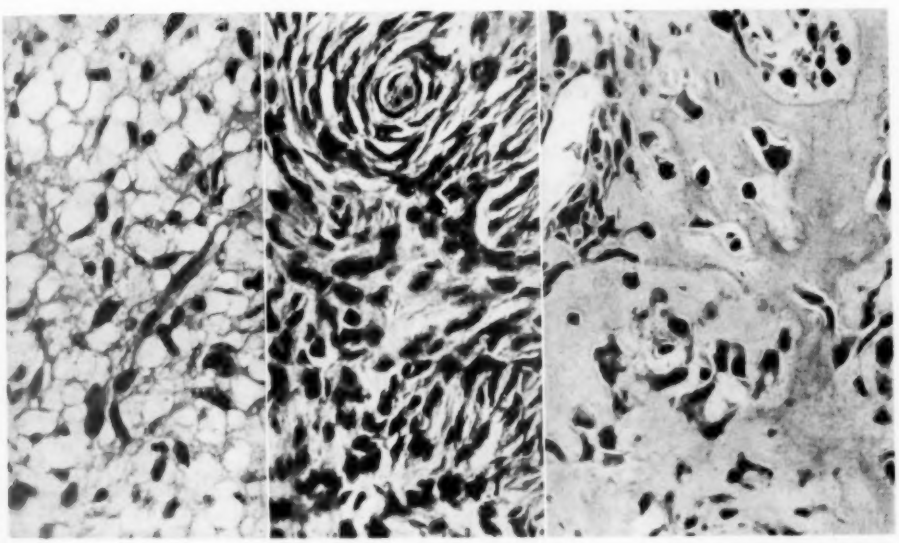


FIG. 2.—Case 1: Mesenchymoma of the deep gluteal tissues. At the left an area of partly differentiated liposarcoma, in the center is differentiated fibrosarcoma. These two are from the primary tumor. At the right is an area of osteogenic sarcoma from the second recurrence.

Case 3.—D. C. (72197). A 70-year-old married Hebrew pattern grader had noted a swelling of the posterior surface of the left lower thigh 4 months before admission to the Presbyterian Hospital. It appeared shortly after he experienced a sharp pain in the left calf. When the pain stopped the tumor remained symptomless and apparently stationary in size. When examined the mass was very firm, irregular in outline, deeply

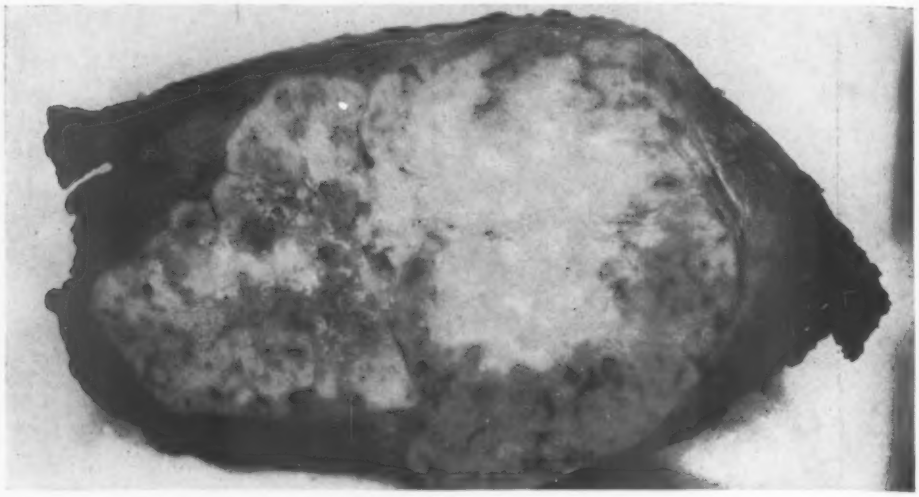


FIG. 3.—Case 2: Mesenchymoma of rectus femoris muscle.

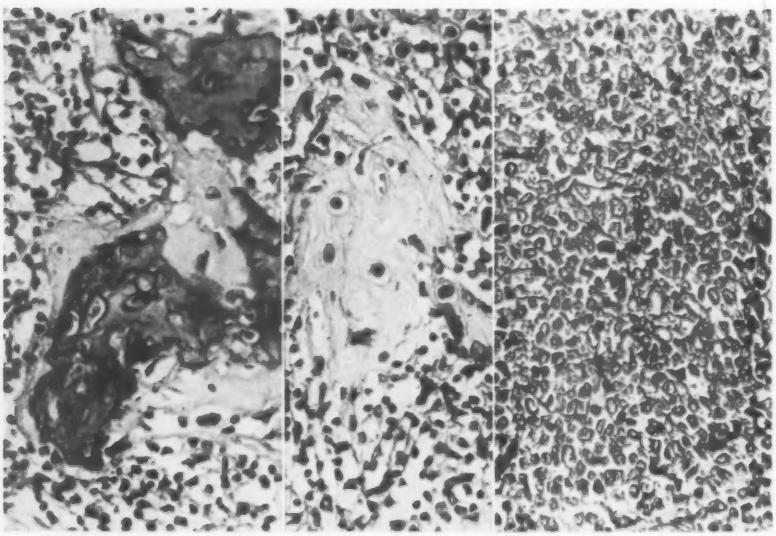


FIG. 4.—Case 2: Mesenchymoma of the rectus femoris muscle. At the left an area of osteogenic sarcoma, in the center chondrosarcoma and at the right reticulum cell sarcoma.

attached and measured 16 x 11 cm. Roentgen examination was negative. At exploration 10/13/39 it was found that the tumor lay in the muscles and deep to them. A biopsy alone was taken. Roentgenotherapy was given through a posterior and two lateral portals. A total of 8200 r measured in air was given from 10/19/39 to 2/5/40. The factors were

200 KV., 25 M.A., T.S.D. 50 cm. filter 1 mm. Cu. and 1.25 Al. The tumor failed to respond and it was suspected of extending upward into the pelvis. He died at home

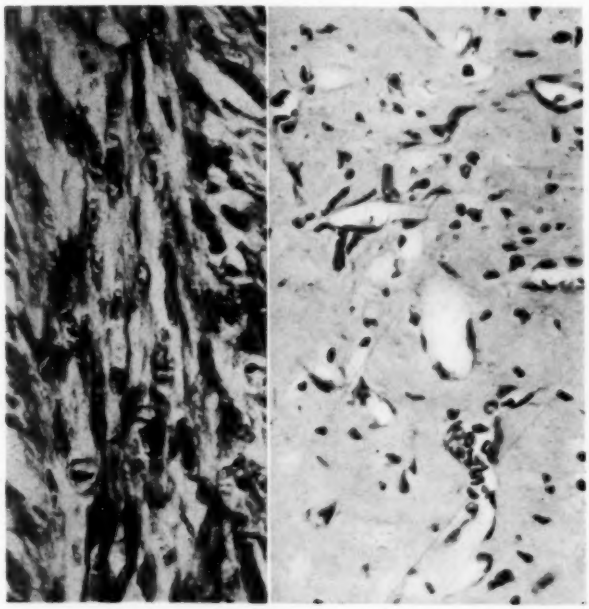


FIG. 5.—Case 2: Mesenchymoma of the rectus femoris muscle. At the left an area of leiomyosarcoma and at the right another area showing angiomatoid proliferation of capillaries.

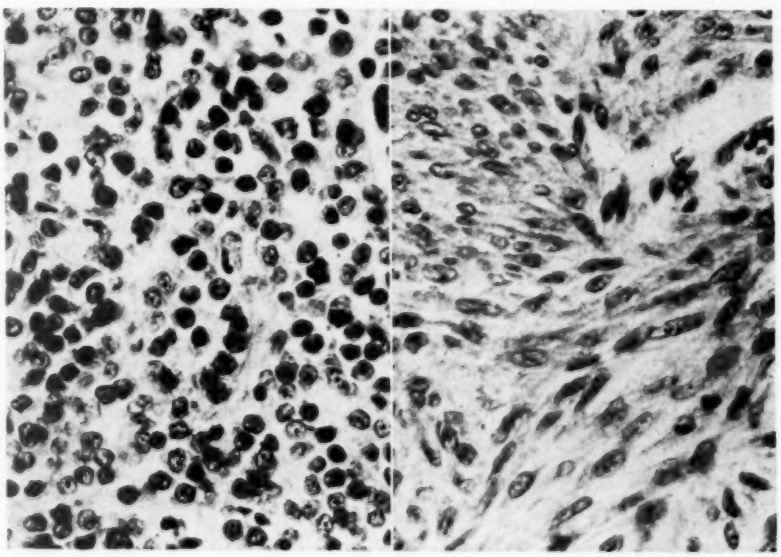


FIG. 6.—Case 3: Mesenchymoma of anterior thigh muscles. At the left an area of reticulum cell sarcoma and at the right fibrosarcoma.

5/25/40, seven months after the beginning of treatment and 11 months after the tumor was first noticed. The biopsy showed in juxtaposition two widely different tumor forms;

a fibrosarcoma and a reticulum cell sarcoma (Fig. 6). (Case mentioned in Stout, A. P.; Sarcomas of the Soft Parts. J. Missouri State Med. Assoc., **44**: 329–334, 1947.

Case 4.—(P.&S. 254457), white female age 62 years. She suffered for two years with backache and was treated with "ovarian hormone." During the last seven months of this period there were attacks of more and less severe vaginal bleeding and when some masses of necrotic tissue were passed a leiomyosarcoma of the uterus was suspected from histologic examination. A total hysterectomy was done without removing the tubes and ovaries. The uterus measured 8.5 x 5.2 x 4 cm. Its cavity was dilated and filled with friable necrotic tumor which invaded the myometrium almost reaching the serosa. The growth was largely leiomyosarcoma with one portion composed of rhabdomyosarcoma. (Fig. 7). (Courtesy of Dr. A. O. Severance, Nix Hospital, San Antonio, Texas). This uterine case is an example of the malignant mixed tumors of the urogenital tract and therefore does not properly belong among the others. It is included solely for comparison.

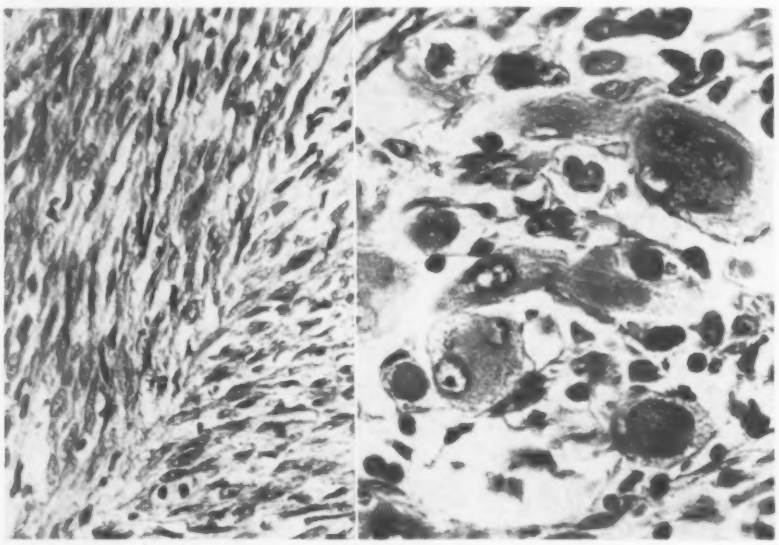


FIG. 7.—Case 4: Mesenchymoma of the uterus. At the left leiomyosarcoma; at the right rhabdomyosarcoma.

Case 5.—(P.&S. 24674). A. L. A male Italian American student age 15 years. Four weeks before admission a mass was noted in the right antero-lateral neck region. It measured 5 x 3 x 3 cm. At operation its upper end was adherent near the angle of the mandible and its lower pole was adherent at the level of the thyroid cartilage. It extended from the anterior border of the sterno-mastoid muscle to within 2 cm. of the midline. The external carotid artery passed through it and was resected with it. The operator felt that it was completely removed. It varied in consistency from almost cartilaginous to fleshy. A series of twenty postoperative x-ray treatments were given from 5/3/46 to 6/12/46 to the right and left sides of the neck, 2950 r to each; 9½ months after excision there was no evidence of recurrence. This tumor showed areas of hemangiopericytoma, leiomyosarcoma and undifferentiated myxoid tissue (Fig. 8). (Courtesy of Dr. G. Y. McClure, Grasslands Hospital, Valhalla, N. Y.)

Case 6.—(P.&S. 24830). A white male age 51 years. The presence of a mass in the right lung field had been known for four years. It was discovered when a roentgenogram was taken during an influenzal attack, and was thought to be a cyst. When a repeat roentgenogram showed that it had doubled in size, operative removal was undertaken. At

operation an encapsulated mass measuring 10.3 x 3.5 x 7.5 cm. was removed from the fissure between the upper right and middle lobes. The tumor was a mixture of fibrosarcoma, hemangiopericytoma, hemangioendothelioma, liposarcoma, and myxoma. (Case of Alston and Paulson).

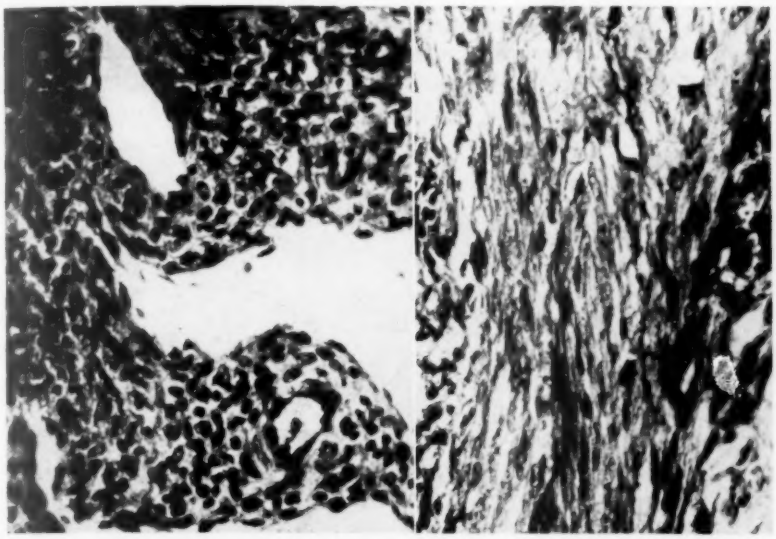


FIG. 8.—Case 5: Mesenchymoma of deep tissues in the lateral neck. At the left hemangiopericytoma and at the right leiomyosarcoma.

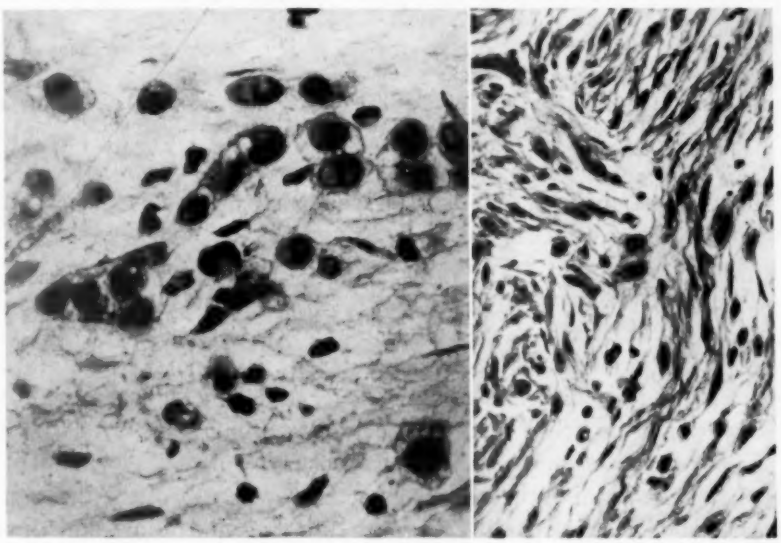


FIG. 9.—Case 7: Mesenchymoma of the leg. At the left rhabdomyosarcoma and at the right fibrosarcoma.

Case 7.—(P.&S. 25181). Female 35 ± years old. An encapsulated nodule was removed from the leg "over the tibia" for cosmetic reasons. It measured approximately 14 x 11 mm. It was made up of a mixture of rhabdomyoblasts and fibrosarcoma (Fig. 9). (Courtesy of Dr. Philip Rosenblatt, the Jewish Hospital, Brooklyn, N. Y.).

Case 8.—(91982). A six-year-old white boy came to the Babies Hospital, New York, because an epigastric mass had been felt on physical examination one week before. The mass lay to the left of the midline, was continuous with the liver and measured 6 cm. in diameter. Roentgen-ray showed that the stomach was compressed and displaced laterally by the mass. 12/7/44 at operation the mass replaced most of the left lobe of the liver projecting from its under surface. The left lobe was resected. There were no evidences of recurrence two years after operation. The tumor was made up of myxoid areas, angiomatous parts and tissue suggesting liposarcoma (Fig. 10). (Case reported by Donovan and Santulli).

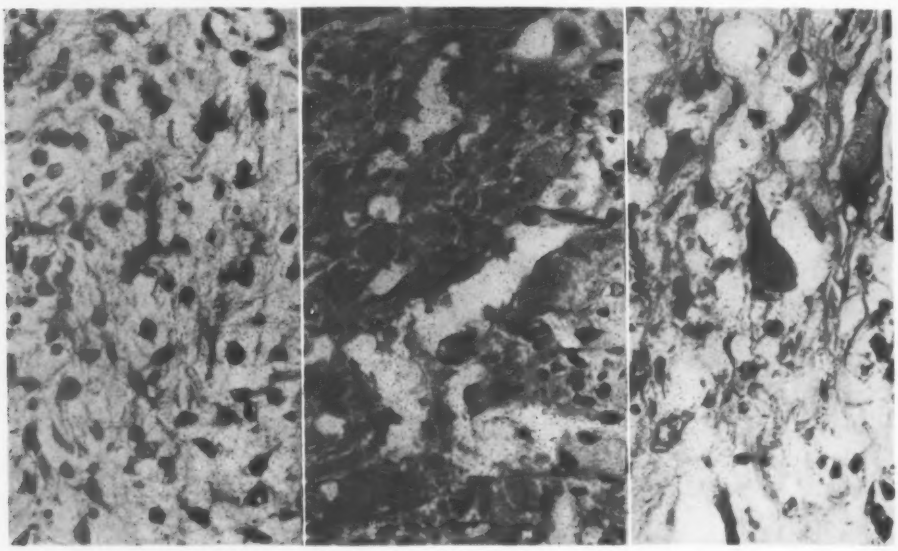


FIG. 10.—Case 8: Mesenchymoma of the liver. At the left myxoma, in the middle hemangioma and at the right liposarcoma.

This group of malignant mixed mesenchymal tumors is of considerable interest because it proves that such amalgamations are not always confined to certain definite regions where congenital malformations are to be expected such as the urogenital tract and breast but may be found in other organs and the soft parts. Whether or not all of them are dysontogenetic growths starting from congenitally misplaced mesenchymal cells is impossible to prove and remains a pure speculation. From whatever cells they may arise, there is some support for the belief that metaplasia plays some part in their development. There is, for example, the classical experiment of Carey (1921) who succeeded in transforming the normal smooth muscle cells of the urinary bladder into striated muscle cells by repeated emptying and filling and there are countless examples of heterotopic bone and cartilage formation due to physicochemical changes in the environment. If such metamorphoses can occur in non-neoplastic cells, it is not difficult to suppose that it may occur in neoplasms.

It would be most reasonable perhaps to call such neoplasms mixed tumors but if that is done it requires another adjective to differentiate them from the epithelium-containing mixed tumors for which that name has long been used

and "mesenchymal mixed tumor" seems an unnecessarily cumbersome term. The word mesenchymoma has already been applied to these tumors by some authors and this appeals to the writer as proper and pertinent. It is necessary to indicate by an adjective whether a given tumor is benign or malignant, since both varieties of the tumor are formed. The group of cases here reported are all malignant mesenchymomas.

So far as treatment is concerned, it is obvious that early and radical excision is essential even if this means amputation. The writer once again wishes to emphasize the importance of biopsy before treatment in all tumors of the soft parts. Only by learning beforehand the nature of the growth can the form of therapy offering the best hope of cure be undertaken at the outset. If the first attempt is inadequate and fails, it is seldom indeed that subsequent attempts will succeed no matter how radical they may be.

SUMMARY

A group of several unusual malignant neoplasms is reported, each one of which is composed of a mixture of malignant tumor forms derived from the mesenchyme and amalgamated into a single mass. Most of these arose in the soft parts. Such tumors belong to a group called mesenchymomas of which there are both benign and malignant forms and which are more commonly observed in the urogenital tract and breast.

REFERENCES

Alston, E. F., and D. L. Paulson: Mesenchymoma of the Pleura, a Case Report. J. Thoracic Surgery (to be published).

Amolsch, A. L.: Mixed Mesodermal Tumors of the Uterus and Vagina with Report of 6 Cases. Am. J. Cancer, **37**: 435–444, 1939.

Carey, E. J.: The Experimental Transformation of the Smooth Bladder Muscle of the Dog, Histologically into Cross-striated Muscle and Physiologically into an Organ Manifesting Rhythmicity. Am. J. Anat., **29**: 341–378, 1921.

Colvin, S. H. Jr.: Certain Capsular and Subcapsular Mixed Tumors of the Kidney Herein Called "Capsuloma." J. Urol., **48**: 585–600, 1942.

Donovan, E. J., and T. V. Santulli: Resection of the Left Lobe of the Liver for Mesenchymoma. Ann. Surg., **124**: 90–93, 1946.

Dreyfuss, M. L., and S. Lubash: Malignant Mixed Tumor of Spermatic Cord. J. Urol., **44**: 314–324, 1940.

Gardner, G. H.: Fibromyoma Angiomatosum of the Uterus. Am. J. Obst. & Gynec., **40**: 822–830, 1940.

Gilmour, J. R. A.: Recurrent Tumor of the Mesenchyme in an Adult. J. Path. & Bact., **55**: 495–499, 1943.

Haagensen, C. D., and A. P. Stout: Synovial Sarcoma. Ann. Surg., **120**: 826–842, 1944.

Hill, R. P., and A. P. Stout: Sarcoma of the Breast. Arch. Surg., **44**: 723–759, 1942.

Hirsch, E. F., and G. W. Gasser: Cancerous Mixed Tumor of the Urinary Bladder. Arch. Path., **37**: 24–26, 1944.

Limburg, H.: Lymphangiocystic Fibroma with Malignant Endothelioma as Hitherto Unknown Mixed Tumor of the Uterus. Arch. f. Gynäk., **174**: 46–63, 1942.

McDonald, J. R., S. W. Harrington and O. T. Claggett: Hamartoma (often called chondroma) of the Lung. J. Thoracic Surg., **14**: 128–143, 1945.

McFarland, J.: Dysontogenetic and Mixed Tumors of the Urogenital Region with Report of a New Case of Sarcoma Botryoides Vaginae in a Child and Comments Upon Probable Nature of Sarcoma. Surg., Gynec. & Obst., **61**: 42–57, 1935.

Mallory, T. B.: A Group of Metaplastic and Neoplastic Bone- and Cartilage Containing Tumors of the Soft Parts. Am. J. Path., **9**: 765–776, (Supp.) 1933.

Masson, P.: Tumeurs mixtes. Atlas du Cancer 3ième et 4ième Fascicules. F. Alcan, Paris, 1924.

Masson, P.: The Role of the Neural Crests in the Embryonal Adenosarcomas of the Kidney. Am. J. Cancer, **33**: 1–32, 1938.

Murray, M. R., and A. P. Stout: Demonstration of the Formation of Reticulin by Schwannian Cells *in Vitro*. Am. J. Path., **18**: 585–593, 1942.

Novak, E.: Gynecological and Obstetrical Pathology. Philadelphia and London, 1940. W. B. Saunders Co.

Plaut, A.: Lymphangiocystic Fibroma of the Uterus. Am. J. Obst. & Gynec., **51**: 842–851, 1946.

Rabson, S. M.: Multiple Mesenchymal Hemendothelioma. Arch Path., **25**: 185, 1938.

Rocher, H. L. and Uzac: Angiome diffuse des muscles antérieurs de l'avant-bras. Gaz. hebd. d. sc. méd. de Bordeaux, **52**: 380, 1931.

Stout, A. P.: Human Cancer. Phila., 1932, Lea and Febiger.

Ibid: Liposarcoma—The Malignant Tumor of Lipoblasts. Ann. Surg., **119**: 86–107, 1944.

Ibid: Tumors of Blood Vessels. Texas State J. Med., **40**: 362–365, 1944.

Ibid: Neurofibroma and Neurilemoma. Clin. Proc., **5**: 1–12, 1946.

Ibid: Tumors of the Peripheral Nervous System. Arch. Soc. Argent. de Anat. Norm. y. Patolog. 1947 (in press).

Ibid: Sarcomas of the Soft Parts. J. Missouri State Med. Ass., **44**: 329–334, 1947.

Takács, F.: Peculiar Tumor Originating in the Uterus (Mesenchymoma Embryonale Angioplasticum). Virchow's Arch. f. path. Anat., **309**: 550–560, 1942.

Tauber, E. B., L. Goldman, and C. Bassett: Mesenchymoma, a New Type of Turban Tumor. Arch. Derm. & Syph., **37**: 444, 1938.

Wilson, H.: Extraskeletal Ossifying Tumors. Ann. Surg., **113**: 95–112, 1941.

630 W. 168th St.
New York 32, N. Y.

LINGUAL GOITER

REPORT OF THREE CASES

EMIL GOETSCH, M.D.

BROOKLYN, N. Y.

FROM THE DEPARTMENT OF SURGERY OF THE LONG ISLAND COLLEGE OF MEDICINE AND THE LONG ISLAND COLLEGE HOSPITAL, BROOKLYN, N. Y.

THYROID ANOMALIES occurring in the tongue are of interest to the surgeon not only because of the practical problems involved in their surgical treatment but also because of their embryologic origin and the various parenchymatous changes to which they are subject. The favored site for the occurrence of thyroid tissue in the tongue is at its pharyngeal portion in the region of the foramen caecum. Aberrant thyroid glandular tissue rarely occurs in the body of the tongue. Tumors arising from this misplaced thyroid tissue have been described and reported under the designation of lingual thyroid, lingual goiter or thyroid tumor at the root of the tongue. These terms are often further qualified by aberrant or accessory. The term lingual thyroid is correctly used when there is a thyroid gland in the neck and when the lingual tissue functions as accessory thyroid. Lingual goiter should be applied to hypertrophic thyroid tissue at the base of the tongue in those instances of nonmigration of the thyroid anlage from the region of the foramen caecum.

In an unusually comprehensive review Montgomery[1,2] gathered all the cases of lingual thyroid nodules reported in the literature through 1936, of which there were 231 possible cases, and of which only 144 were personally authenticated and accepted by him. Of these 144 cases there were 142 instances in which the lesion occurred on the dorsum of the tongue and only two instances in which the thyroid tissue developed in the body of the tongue. Among these lingual thyroid nodules, there was one case of his own, reported by Montgomery. The criteria of authenticity accepted by him were (1) the examination of the specimen removed which should reveal thyroid gland tissue, or in lieu of this requirement; (2) thyroid insufficiency should supervene following removal of the nodule; and, finally, (3) the lesion should appear in the substance of the tongue between the epiglottis and the circumvallate papillae.

Montgomery reported only those cases in which the lingual thyroid tumor was causing symptoms. The incidence of thyroid tissue originating in the median anlage and not producing symptoms will doubtless never be established. Montgomery's[2] review subsequently appeared in a monograph to which reference should be made for an analysis of case reports appearing in the literature to 1936. Shortly after this review appeared, Buckman[3] published a summary of case reports to and including 1935. He included in his tabulation 242 cases including one of his own. There is a marked discrepancy in the number of cases reported by these two authors. This is probably due to the fact that the criteria of authenticity adopted by Montgomery were evidently not those of

* Presented before the New York Surgical Society, November 13, 1946.

Buckman who included at least 32 cases in his series which did not meet the criteria of Montgomery.[2]

It seems that Hickman's[4] case of congenital tumor of the base of the tongue, published in 1869, and authenticated by Montgomery, is the first case on record of a lingual thyroid nodule. Bernays,[5] in 1888, removed a lingual thyroid tumor substantiated by histologic examination. A fairly extensive search of the literature revealed approximately 14 cases of lingual thyroid nodule for the period 1936 to 1945, inclusive. Some of these case reports are unusually brief and lacking in sufficient pathologic data to be completely authentic. Some possibly have escaped notice because they were published under designations other than lingual thyroids.

It is the purpose of this report to review three cases of lingual goiter operated upon by the author, at the Long Island College Hospital. They are added to the cases reported in the literature in the hope that they may prove of interest not only because of their symptomatology and surgical treatment but also in view of their histologic findings.

CASE REPORTS

Case 1.—Miss A. L., age 30, stenographer, was first seen February 2, 1933. She was admitted to the Long Island College Hospital February 4, 1933, and discharged February 18, 1933.

The principal complaints included difficulty in swallowing, severe choking attacks and a change in the voice. Since her childhood the patient's voice had been husky, low-pitched and "throaty." Swallowing was accomplished with increasing difficulty. This caused her to "gulp" her food. Frequent attacks of choking were provoked by swallowing solid foods. Eating became a source of great anxiety. During the past four years, there had been a gradual loss of 12 pounds in weight. Two years previously, she had had a severe choking spell, caused by eating a sandwich. She had become extremely nervous and because of belching and certain abdominal complaints, appendicectomy was performed. The choking attacks gradually became more frequent and more serious, and she had to resort to free draughts of water to aid in swallowing. Four months previously, she had had an alarming attack following the eating of an apple, and this was followed three days later by another attack. Shortly before her first visit, she had had a severe choking spell, unprovoked by eating. For a considerable period, there had been a constant feeling of "tightness" in her throat, and during the choking attacks she suffered from severe dyspnea and palpitation. She became "panicky" and at times felt that she was "passing-out."

Normal menstruation began at the age of 12. During the six months previous to her examination, the menstrual periods had become irregular, scantier, and of two days' duration. Her general health had been good.

The patient was an alert, well-nourished, undersized young woman, whose speech had a peculiar "throaty" quality. The ocular reactions were normal, the palpebral clefts were approximately equal and there was no exophthalmos. With the tongue protruded well forward a submucosal nodule approximately the size of a golf ball, was located centrally on the dorsum of the tongue posterior to the region of the foramen caecum. It protruded from the surface, impinged upon the posterior pharyngeal wall and continued downward to the tip of the epiglottis, markedly compromising the pharyngeal air space. With the exception of a few irregularities, the surface of the tumor was smooth. It was red in color and appeared hypervascular. It was impossible by laryngoscopic examination to obtain a view of the larynx which was obscured by the superimposed mass. A small papilla, centrally located on the superior surface of the tumor, was noted. It was firm, elastic in consistency and measured 2 mm. in diameter. A diagnosis of lingual thyroid nodule was made.

The general physical examination was negative. A cervical thyroid gland could not be palpated. In the midline of the neck, above the hyoid bone, a diffuse prominence suggesting pressure from the throat was seen. There was no tremor. The pulse was 82, the systolic blood pressure 110 mm. Hg., and the respirations 20 per minute. Weight 112 pounds. The temperature averaged 97.8° F. The blood counts and the hemoglobin determinations were all within normal limits.

The urine was negative. The basal metabolic rates taken on two successive days were −22 per cent and −21.4 per cent, respectively. A comparison of the patient's height with that of both parents, two adult sisters and one brother revealed that she was definitely undersized and the smallest in the entire family.

Operation.—February 6, 1933: Partial excision of a lingual thyroid, under ether anesthesia. Preliminary hypodermic injections of morphine were administered. The patient became drowsy and the pulse depressed, in keeping with the increased response to morphine and ether in patients with hypothyroidism as compared to those with hyperthyroidism. Ether vapor was administered through a nasal catheter. The head was placed in full hyperextension. Three sutures of braided silk were used; one was placed through the tip of the tongue and one on each side posteriorly through the entire substance of the tongue. By traction upon these sutures the tongue could be drawn out and with digital pressure the tumor could be brought well forward and satisfactorily exposed. The nodule was approximately as large as an ordinary egg and was covered by the mucous membrane of the tongue. It was oval in shape with its long diameter running anteroposteriorly. At the anterior pole a definite dimple indicating the position of the foramen caecum was recognized. The overlying mucous membrane was bright red in color and large veins were seen coursing over the lateral margins of the mass. Occasionally, the respirations became somewhat embarrassed due to pressure on the epiglottis and larynx. The difficulty was overcome by exerting digital pressure behind the tumor. Four heavy, braided, transfixion ligatures were placed transversely through the substance of the tongue below the tumor mass. The farthest posterior was placed with some difficulty immediately above the epiglottis. With good exposure obtained, a lenticular incision was made on each lateral margin of the tumor beginning well posteriorly and carried forward so that the junction of the two incisions included the foramen caecum. A margin of mucous membrane, three-quarters of a centimeter in width, was allowed to remain attached to the lateral borders of the tumor. Immediately under the mucous membrane of the tongue, the surface of the tumor was exposed. It appeared to be glandular tissue of pink color and cellular appearance. The tumor was clearly defined from the normal lingual musculature of the tongue and had a limiting membrane or pseudocapsule. A generous wedge of tissue was removed by cutting downward slightly beyond the midportion of the tongue. In order to avoid complete excision margins of glandular tissue on the lateral aspects were allowed to remain. Hemorrhage was not extensive. The heavy transfixion sutures, previously placed through the tongue and beneath the tumor, were then snugly tied. Additional approximating sutures of chromic catgut were used. The transfixion sutures were left long for purposes of traction in case of emergency. The tongue now appeared somewhat edematous but there was no serious respiratory embarrassment.

Immediate inspection of the specimen showed that it included the foramen caecum. The parencyma of the tumor resembled that frequently seen in a partially degenerated adenoma of the "fetal" type. It had a glistening, relatively homogeneous, pale-yellowish appearance and contained a moderate amount of colloid. Toward the anterior pole of the specimen, there was an area of degeneration. Specimens of the tumor were placed in formalin.

Postoperative Course.—Recovery was uneventful. The rectal temperature was 101.8° F. and the pulse 122 on the evening of the day of operation. Five days after operation, under light anesthesia, the silk transfixion sutures were removed. The patient was discharged 12 days after operation, with normal temperature, pulse and respirations. The basal metabolic rate on February 16th was −32.9 per cent.

Gross Pathology.—The specimen of a lingual thyroid tumor weighed eight Gm., and

measured 2.5 x 3 x 3 cm. The superior surface was covered by mucous membrane and presented a slightly lobular, irregular surface. On the superior surface, eccentrically placed, there was a minute depression which probably represented the site of the foramen caecum. On the inferior border of the specimen, some reddened, hemorrhagic muscle fibers were seen. The cut-surface of the tumor proper presented a lobular appearance, a pinkish-yellow color and a smooth homogeneous structure grossly resembling the appearance of a fetal adenoma. A moderate amount of stroma was present and in one area the tissue resembled the appearance of normal thyroid gland.

Microscopic Examination.—The superior surface of the section was covered by normal stratified squamous epithelium characteristic of the lingual mucosa. Toward the anterior extremity of the specimen a blind tract was seen leading downward a considerable distance below the surface. This tract represented the foramen caecum and the rudimentary thyroglossal duct (Figs. 1 and 2). Below the lingual mucosa there was a wide zone of hyalinized fibrous tissue, which anteriorly contained groups of epithelial cells, some of which were seen to form small and large colloid-containing follicles characteristic of normal thyroid tissue. The acini were of irregular size, without definite architecture, and were lined by cuboidal or low columnar cells, the nuclei of which were deeply stained. A pink-staining colloid filled the follicles.

In the fibrous zone adjoining the capsules of the several nodules composing the tumor proper, lamellated layers of thyroid follicles fairly normal in appearance were seen. Immediately under the capsules there was a distinct difference in the type of tissue composing the nodules. It very closely resembled that frequently seen in fetal adenoma (Fig. 3). The bulk of the nodules was composed of large numbers of small and medium sized follicles simulating the appearance of normal thyroid but without definite architectural arrangement (Fig. 4). Toward the center of the tumor there was an area of degeneration in which the follicles were quite irregular in shape and varied greatly in size. They were separated by a fibrous and myxomatous ground substance, such as is often seen in adenomatous goiter (Fig. 5). In the center of the largest nodule composing the tumor there was an area of fibrosis, necrosis and hemorrhage.

In the area of greatest depth of the tumor the thyroid tissue appeared as solid groups or cords of cells and as large numbers of very minute follicles with a sparse intervening stroma. This tissue presented no definite architecture. The nuclei were deep-staining and hyperchromatic. The parenchyma presented the appearance characteristic of the cellular fetal adenoma (Fig. 6).

The deeper portions of the rudimentary thyroglossal duct were lined by transitional epithelium possessing a ciliated border (Fig. 7). In the fibrous tissue surrounding the duct there was a considerable infiltration of lymphoid cells. *Pathologic Diagnosis:* Lingual goiter of the fetal adenomatous type.

Progress Notes.—March 6, 1933: Since her discharge from the hospital February 18th, the patient had been taking thyroid extract one grain twice daily. She was conscious of some tightness in her throat. The voice was clear, and a slight Chvostek sign was noted on the left side. The pulse was 92. There was no tremor. Her weight was 106 pounds. The basal metabolic rate was −15 per cent. Two thyractin tablets, containing one-half grain of thyroid extract each, were prescribed daily.

March 27, 1933: A small, rounded elevation was noted at the site of the original tumor, and the operative incision had almost entirely healed. The pulse was 90, and the weight 107 pounds.

April 10, 1933: The patient had been taking one-half grain thyractin tablets twice daily for the previous 35 days. As a result, she became more energetic and alert, and felt generally improved. The voice was clear, she swallowed with ease and stated that she had lost the taste of sweet but not of sour articles. There was a slight increase in the pulse rate to 96 beats per minute. Her weight was 106.5 pounds, and the basal metabolic rate had increased from −15 per cent to +7.4 per cent. During the following two months, the therapy was reduced to one-half grain of thyroid extract per day. Because of some nervousness it

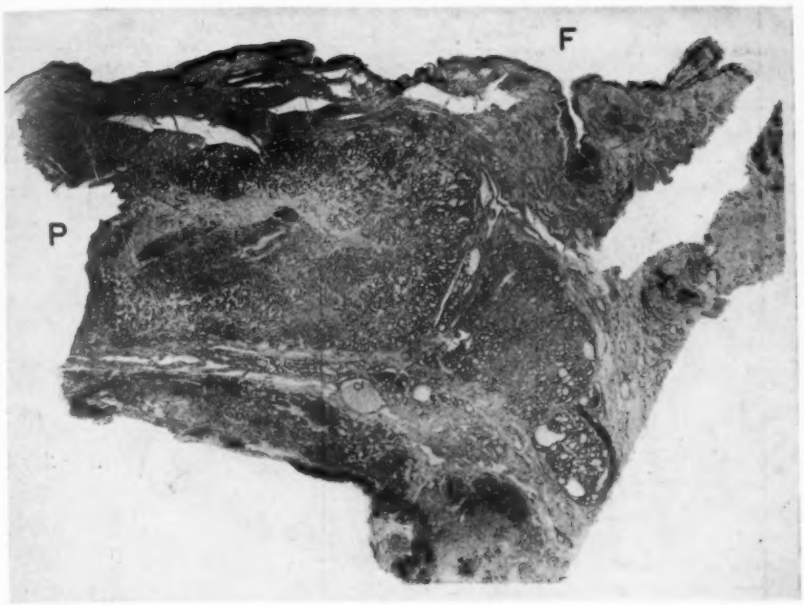


FIG. 1.—Case 1: Photomicrograph of a sagittal section through the entire specimen of a lingual goiter from a woman 30 years of age. Note anteriorly the foramen caecum (F) and the rudimentary thyroglossal duct. Note the encapsulated nodules which showed multiple types of parenchymatous overgrowth and the large area of myxomatous degeneration in the center of the largest nodule. The posterior pole (P) was transected and allowed to remain *in situ*. (×4.5)

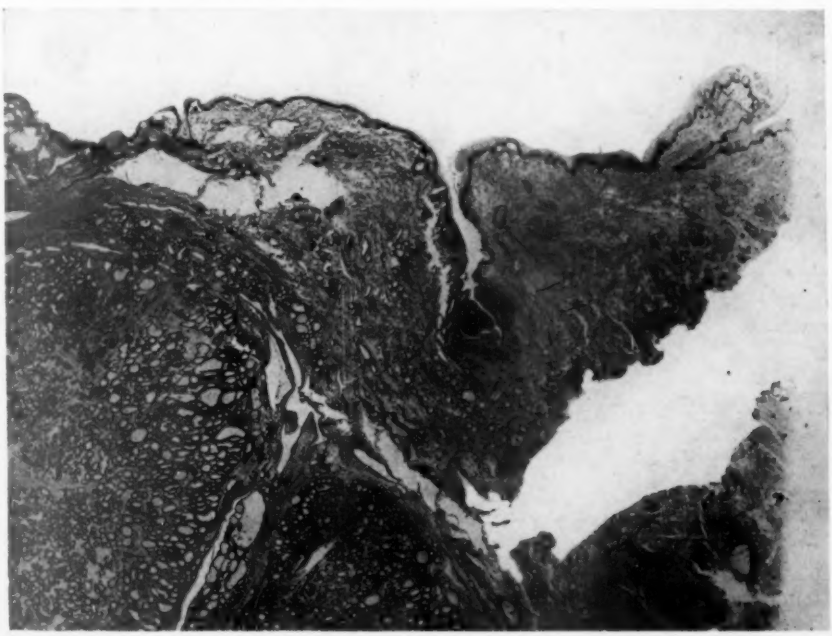


FIG. 2.—Case 1: Greater magnification, photomicrograph of an area of section shown in Figure 1. Note the irregularly-scattered thyroid follicles in the submucous fibrous zone and the various types of parenchymatous proliferation in the encapsulated nodules composing the lingual tumor. (×9)

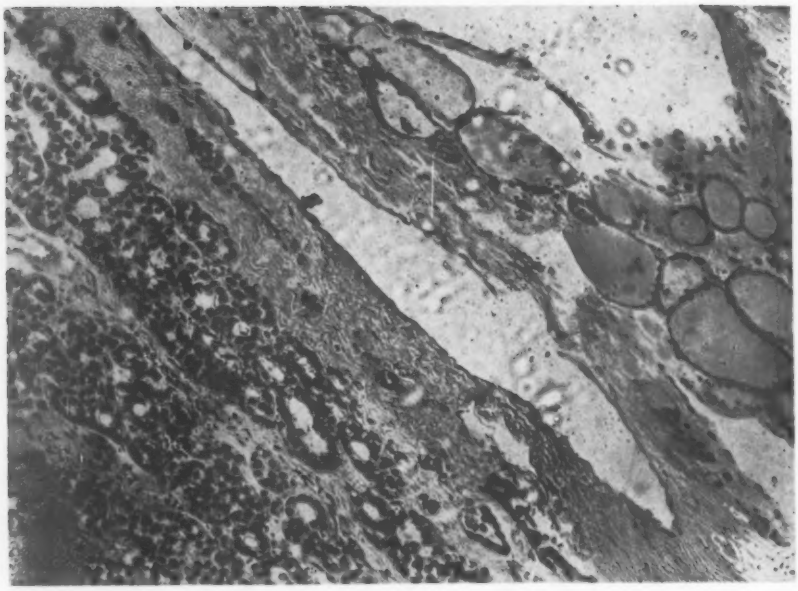


FIG. 3.—Case 1: Photomicrograph of normal-appearing thyroid follicles in the fibrous stroma adjoining the capsule of the lingual nodule. Below the capsule one sees a sudden transition to the fetal type of thyroid, often seen in adenoma of the cervical thyroid gland. (× 125)

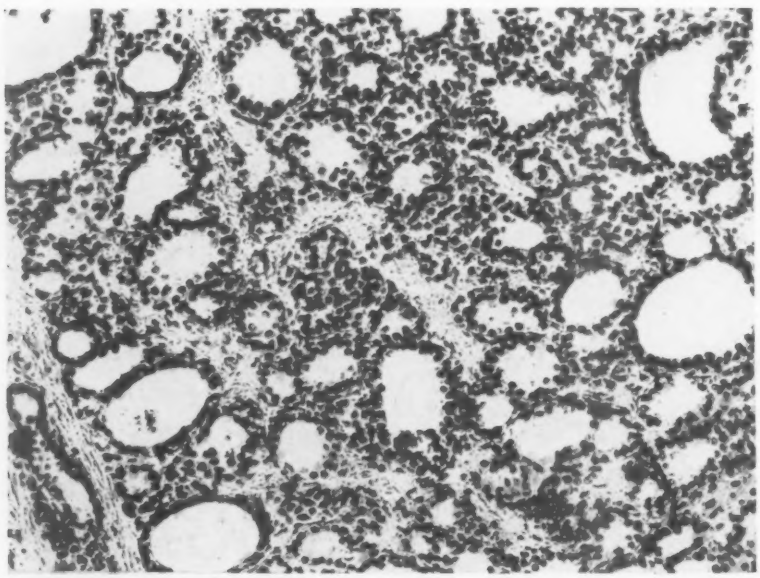


FIG. 4.—Case 1: Photomicrograph illustrating a fairly normal type of thyroid parenchyma found in the lingual nodule. The follicles vary greatly in size, the epithelial cells are cuboidal and the nuclei are rich in chromatin. Note the lack of definite architectural arrangement. (× 125)

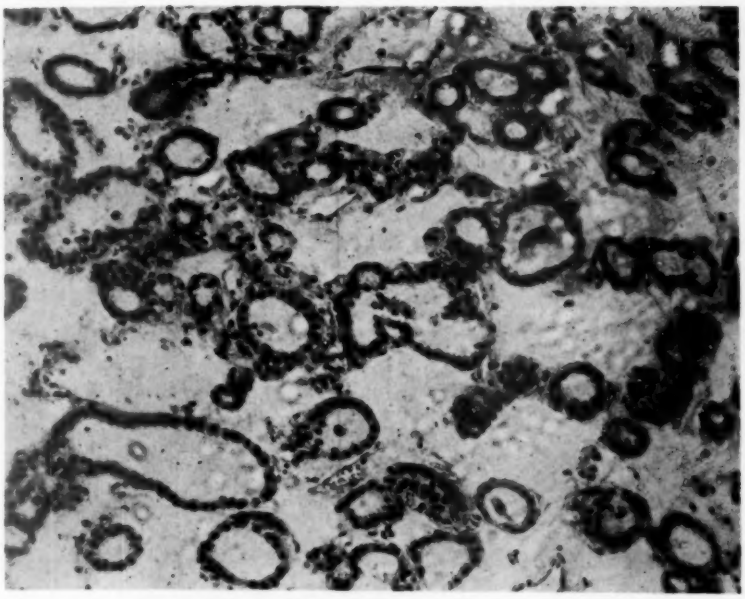


FIG. 5.—Case 1: Photomicrograph showing the type of tissue found in the center of the lingual tumor. The acini of irregular shape and size are separated by a myxomatous stroma characteristic of many cervical thyroid adenomas. This area bordered on a zone of necrosis and hemorrhage. (× 125)

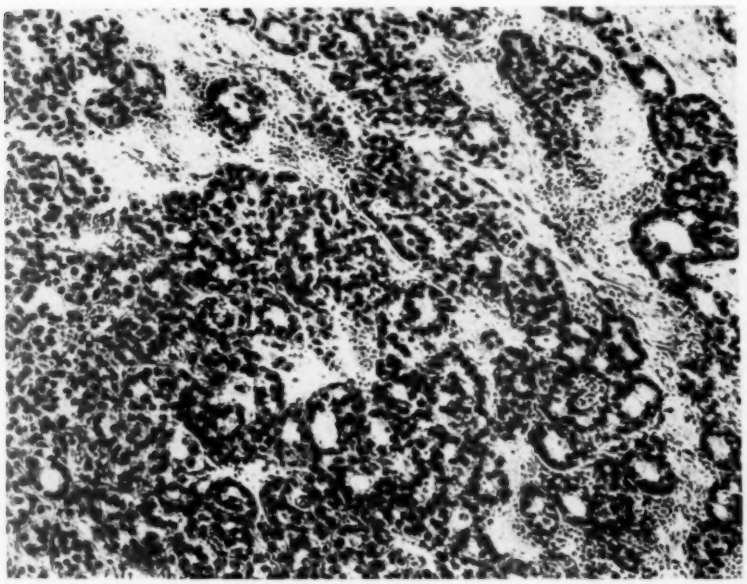


FIG. 6.—Case 1: The parenchyma in the depth of the lingual tumor presents the appearances characteristic of the cellular fetal adenoma. The compact masses of cells, the cellular cords and the minute follicles are lacking in definite architecture. (× 125)

was further reduced to one-half grain of thyroid extract twice a week. One month later, on July 8, 1933, the basal metabolic rate had fallen to −25.8 per cent. Therapy with thyroid extract was increased to one-half grain on alternating days, for 14 weeks, after which, on October 19th, the patient was again examined. She was greatly improved. The clinical symptoms of hypothyroidism had disappeared. She was instructed to continue her previous medication. After three months on this regimen, on October 12, 1933, the basal metabolic rate was −31.6 per cent. Two months later (December 20, 1933) the rate was −13.7 per cent. Thyroid extract in doses of gr. 1 to gr. 1.5 daily was prescribed. The basal metabolic rate two years later, on December 19, 1935, was −5.6 per cent.

Revisit.—April 18, 1936. During the previous three years, the patient had been given thyroid therapy as indicated, and had felt rather well. There were no signs of hypothyroidism. The throat appeared normal. The menses had been normal. The weight was 110.5 pounds. Thyroid extract gr. 1, and iodostarine gr. 5, daily were prescribed.

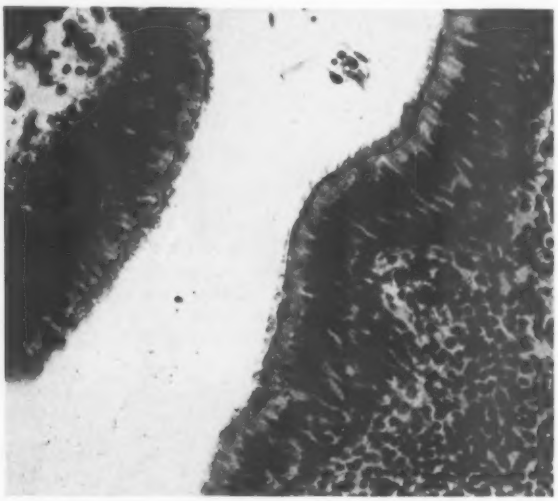


FIG. 7.—Case 1: Photomicrograph showing the ciliated border of the transitional epithelium lining the rudimentary thyroglossal duct. (× 600)

Revisit.—March 13, 1946: The basal metabolic rates taken on seven occasions, between February, 1940, and March, 1945, varied between −13.7 per cent and +10 per cent with an average of −8.2 per cent. During the previous several years, her health had been good. She continued her occupation as a secretary until January, 1946, and then had felt unable to continue. She had occasional periods of nervousness with a feeling of tightness of the throat. She had married in March, 1937, four years after her operation. She became pregnant in January, 1940. The pregnancy was normal, but the fetus, due to complications of the cord, died during the eighth month. The menopause commenced in 1941, when the patient was 39 years of age. Thyroid medication had been continued in the dosage of gr. 1 and gr. 1.5, on alternating days during the preceding ten years with the result that she had continued to feel well. The basal metabolic rates had varied during this time but were constantly slightly below zero, between −2 and −10 per cent, but never reached the low of −17 and −20 per cent previously mentioned. There had been no signs of hypothyroidism. Her weight was 117.5 pounds, which represented a gain of seven pounds since her visit in 1936. The throat was clear and there were no irregularities posteriorly on the dorsum of the tongue. A slightly positive Chvostek sign was elicited on the left.

During her pregnancy she had experienced extreme numbness and pain in the hands, with lack of strength in the fingers. The feeling of tightness in the throat, a mildly positive Chvostek sign and poor dentition with gum recession appeared to point to a very mild hypoparathyroidism, and a chemical examination of the blood revealed in milligrams per 100 cc. of blood: Cholesterol 320; cholesterol esters 188; calcium 10.2; phosphorus 2.8; phosphatase 1.8. The basal metabolic rate was −14 per cent. She had had no iodine medication during the past several years. Medication with thyroid extract gr. 1 alternating with gr. 1.5 daily was advised together with dicalcium phosphate and calcium gluconate with vitamin D.

COMMENT.—It would be correct to designate the lingual thyroid nodule in this instance as a lingual goiter, for on gross and microscopic examination it was found to have the structure, not of normal thyroid gland but of that commonly seen in adenomatous goiter involving the cervical thyroid. There was the tendency to the formation of nodules with pseudocapsules in which there was a scattering of small acini. This might be interpreted as invasion. The parenchymatous overgrowth showed a multiplicity of histologic pictures. There were areas of normal-appearing thyroid adjoining large areas of cellular hyperplasia of the fetal pattern. With and without the formation of minute acini and without definite architectural arrangement, these findings add to the difficulties of pathologic diagnosis.

The nodule must have been present since childhood, for in the early years the voice had been husky, swallowing was difficult and there had been frequent choking attacks. There was evidently an associated hypothyroidism, for the patient was under-sized and, finally, when she presented herself at the age of 30, her metabolic rate registered −22.5 per cent. A cervical thyroid was not palpable. The lingual thyroid was doubtless the only thyroid tissue the patient possessed because after partial excision of the tumor, a moderately severe hypothyroidism intervened. It could hardly be called myxedema. Therapy with thyroid extract in dosage of gr. 1 twice daily was instituted immediately following operation. After a brief interval symptoms of a mild hypothyroidism followed. The basal metabolic rate over the years had risen from the preoperative level of −22.5 per cent to +7.4 per cent. The maintenance dosage of thyroid extract was finally found to be gr. 1 to gr. 1.5 daily. On this regimen her health was well-maintained for the past ten years or more. The basal metabolic rates, determined annually during this period, averaged −6.0 per cent. The patient was married in March, 1937, and became pregnant three years later. It would appear that ovarian function had not been disturbed by the long period of hypothyroidism from which the patient had suffered.

Case 2.—I. C., a female child, age 12, was admitted to the Long Island College Hospital September 19, 1925, and discharged October 23, 1925. The chief complaints were slowness of speech and the presence of a tumor mass on the posterior dorsum of the tongue. The family history was negative for thyroid or other endocrine disorders, and the patient's general health had been good. She began to walk and talk at the average age and did well at school. Menses had not begun.

One month before the patient was admitted her father had had his attention drawn to a peculiarity in the child's speech which sounded as though she "had something" in her mouth. Upon examination of the child's throat he noted a swelling at the base of the tongue.

During the month preceding the child's admission the swelling apparently had increased in size and the impediment in speech had become more noticeable. There were no subjective symptoms such as pain or unusual difficulty in swallowing.

The patient was a well-nourished girl with a somewhat apathetic expression. She did not appear precocious, responded fairly readily and was evidently attaining puberty as evidenced by the appearance of axillary and pubic hair and by the normal development of the breasts. She did not present appearances of any endocrine disorder.

Upon examination of the throat, with the tongue well protruded, a mass was revealed in the region of the foramen caecum. The tumor occluded the space between the anterior

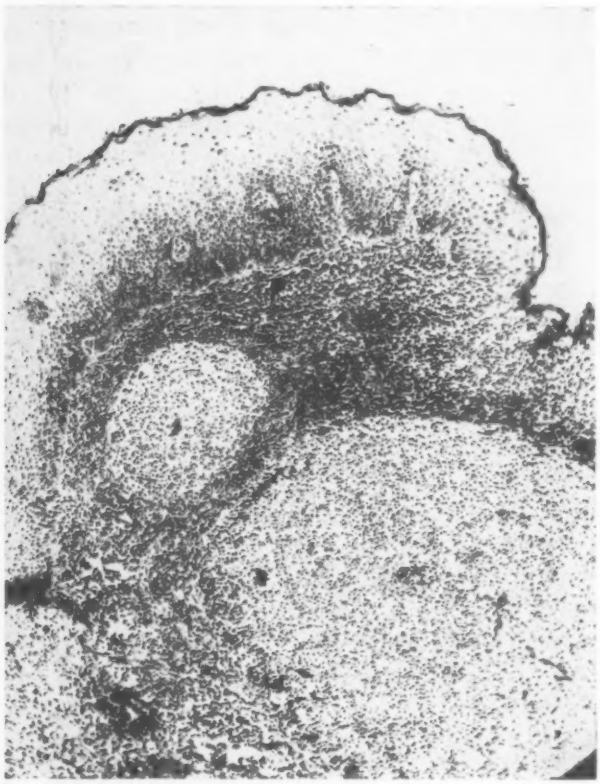


FIG. 8.—Case 2: Photomicrograph showing the surface mucosa and the submucous zone of lymphoid tissue overlying the lingual goiter from a girl 12 years of age. Her principal complaint was an impediment in speech. (×85)

tonsillar pillars and the soft palate. Anteriorly it extended to the centrally located circumvallate papillae and its base was almost equal to the width of the tongue itself. The tumor was elevated from one-half to one centimeter above the surface of the tongue and was relatively smooth and dark-red in color. It appeared to be highly vascular, as indicated by many dilated veins on its surface. The tracheal rings and the cricoid and thyroid cartilages were readily palpated. A cervical thyroid gland could not be palpated. The abdomen was prominent, but otherwise negative. The temperature was 99.6° F., pulse 96, and respirations 21. Blood pressure 95/55. Blood and urine examinations revealed nothing noteworthy.

The impression gained was that we were dealing with an aberrant lingual thyroid nodule and the absence of a cervical thyroid.

Biopsy of Lingual Tumor.—September 21, 1925: Under ether anesthesia, the tumor at the base of the tongue was brought well into view by digital pressure deep in the pharynx. Deep transfixion ligatures of medium size were placed around and below the midportion of the tumor, thus, circumscribing the area from which the biopsy was to be taken. With each puncture of the needle, there was some brisk bleeding, controlled by simple pressure. Incision was made over the dome of the tumor, which was covered by a thin layer of mucous membrane and apparently some fibers of the intrinsic muscles of the tongue. After incision through the outer zone of the tumor a cellular, glandular-appearing structure was encountered. A section was removed for microscopic study. Ligation of the transfixion ligatures, previously placed, controlled all bleeding.

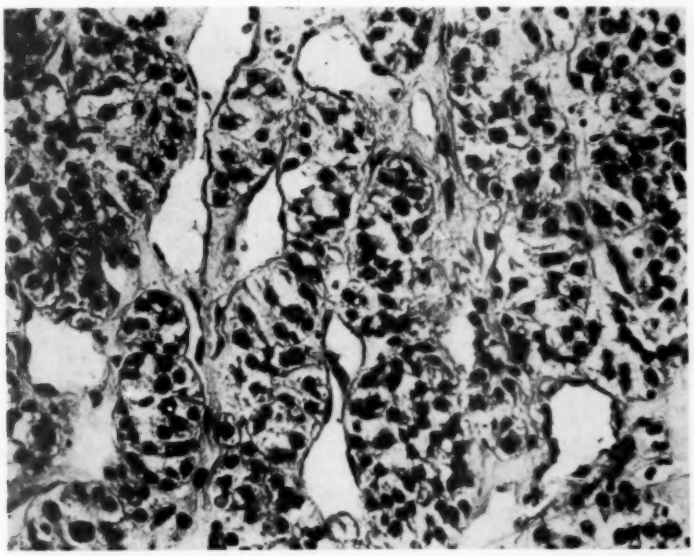


FIG. 9.—Case 2: Photomicrograph of a section from the biopsy specimen of lingual goiter. Note the epithelial cords separated by large sinusoidal spaces and without acinar formation; a picture not uncommonly found in fetal adenoma of the cervical thyroid. (× 300)

Microscopic Examination.—The biopsy showed a thick surface layer of stratified squamous epithelium characteristic of the lingual mucous membrane. Immediately below the mucosa, there was a broad zone in which there was an abundance of lymphoid tissue in diffusely scattered areas and containing several unusually large lymphoid follicles (Fig. 8).

The tumor proper showed two types of epithelial structures. In part, the tissue was composed of irregular, oval, and elongated groups and cords of cells separated from each other by minute connective tissue septa containing blood capillaries. There was no attempt at the formation of follicles and nowhere was colloid to be seen. The cells were fairly large. They showed finely granular cytoplasm with centrally placed large, rounded and oval nuclei, which were deeply stained and rather rich in finely granular chromatin.

The second type of tissue was characterized by irregular groups and cords of cells which were separated by rather large endothelial-lined sinusoidal spaces containing a few red corpuscles. There was a minimum of connective tissue lining the cords and containing numbers of small blood vessels. These cellular cords were composed of irregularly placed, clear cells, with vacuolated, spongy appearing cytoplasm. The nuclei varied greatly in

size. Some were strikingly large, rounded or oval, and rich in chromatin (Fig. 9). *Pathologic Diagnosis:* Lingual thyroid tumor.

Recovery from the anesthesia and the operation was prompt. There was a postoperative febrile reaction accompanied by swelling of the submaxillary nodes due to infection of the operative area. A low grade fever continued for one week, followed by some necrosis and sloughing of tissue at the operative site. Two weeks after the biopsy operation, the infection and edema of the tongue and submaxillary nodes were definitely subsiding. The general condition of the patient was good. There was no dysphagia but the impediment in the voice was more marked. The sutures were extruded spontaneously.

Partial Excision of a Lingual Thyroid Tumor.—October 16, 1925: The patient was anesthetized with ether vapor. The jaws were held well apart by means of a mouth gag and the tongue was drawn well forward by means of traction upon a heavy silk ligature

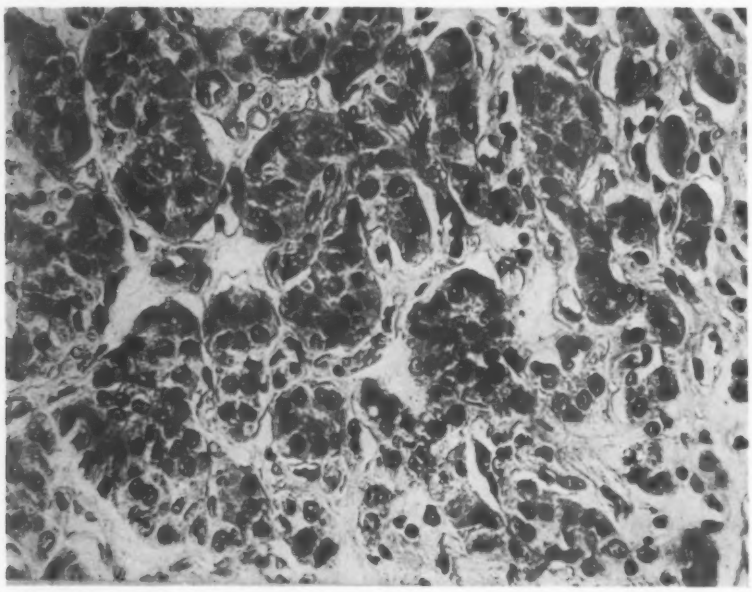


FIG. 10.—Case 2: Photomicrograph showing the principal type of tissue of which the body of the lingual goiter was composed. There is no tendency to the formation of follicles. (× 300)

through the tip of the tongue. A satisfactory approach to the tumor was thus obtained. The separation of a large piece of necrotic tumor tissue was followed by moderate bleeding. By means of digital pressure the tumor was brought well into view. It had a sessile base which was constricted by means of a circumferential suture placed as low as possible, whereupon, the large superior bulging portion was removed. This was followed by a moderate amount of bleeding, which was controlled by long, transfixion ligatures the ends of which were brought out of the mouth. The pharynx was then explored and it was found that the tumor extended posteriorly almost to the epiglottis and appeared to extend downward into the right superior portion of the anterior cervical triangle. It seemed that a more extensive removal of the tumor could only be accomplished by an external approach in the submandibular region. The excised tissue which was firm, cellular and vascular, was composed of masses of parenchyma, resembling adenomatous thyroid. A considerable residue of tumor necessarily remained *in situ*. The specimen was placed in formalin.

Pathologic Examination.—Gross: The specimen represented a portion of the tumor removed from the base of the tongue. It measured 4 cm. in long diameter and 1.5 cm. in

width. No capsule was evident and the tumor obviously had not been entirely removed. The superior surface of the specimen was covered by an irregular mucous membrane with soft, nodular elevations. Upon section, the central portion of the specimen was soft, semi-translucent and glistening and resembled myxomatous tissue. In some portions of the tumor, small bundles of muscle fibers were seen. A scant amount of connective tissue stroma was present.

Microscopically, sections of the tumor presented essentially the same structure as the biopsy. There were two main types of glandular epithelium. The first composing the bulk of the specimen, was characterized by large groups of cells and cords separated from each other by minute strands of connective tissue and narrow spaces lined by endothelium. The protoplasm of the cells was abundant, homogeneous, finely granular and pink-staining. The nuclei were large, round or oval, rich in chromatin and, in general, centrally placed in the cells. There was no definite tendency to the formation of colloid containing alveoli (Fig. 10).

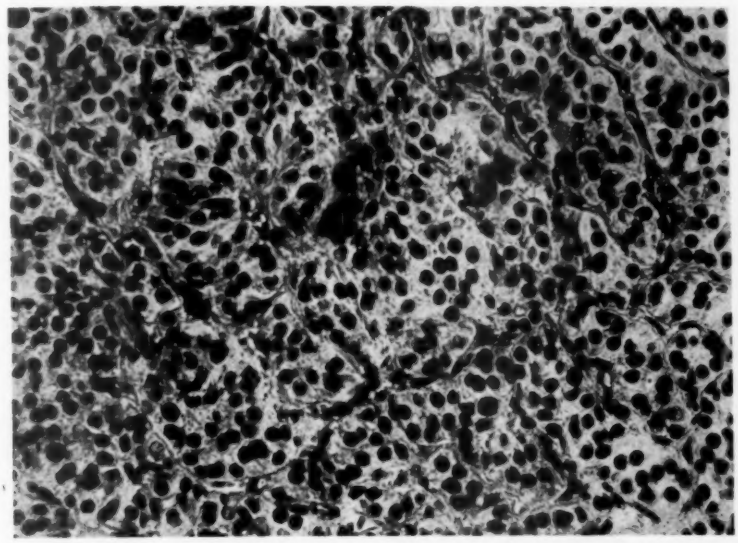


FIG. 11.—Case 2: Photomicrograph showing another type of epithelial growth occurring in large areas of the lingual nodule. Note the resemblance to the structure of parathyroid gland. The preliminary diagnosis of parathyroid tumor was in error. (× 300)

The second principal type of glandular epithelium composing the tumor resembled in many respects the structure of parathyroid gland (Fig. 11). The tissue was compact and composed of irregular groups of cells and elongated cellular cords separated from each other by a minimum of stroma and slit-like endothelial spaces. The cytoplasm of the cells was fairly clear, finely granular, nonvacuolated, and the nuclei were large, centrally placed, rich in chromatin and dark-staining. There was no tendency to acinar formation and colloid was not visible. These epithelial areas were circumscribed by wide zones of dense fibrous tissue in which were seen islands and cords of epithelial cells without definite organization.

The superior portion of the tumor showed a large, thick, superficial zone of granulation tissue containing extravasated blood and large numbers of polymorphonuclear leukocytes. This superficial zone of infection resulting from the biopsy extended downward into the deeper portions of the tumor, and finally ended in a wide zone of dense fibrous tissue which circumscribed the glandular portions of the tumor proper.

A section of the biopsy tissue, fixed in an osmic acid preparation and stained with acid fuchsin and methyl green, showed numbers of small follicles and some fairly large ones

containing a green-staining homogeneous, vacuolated colloid. The follicular cells were low columnar in type and contained a scant amount of cytoplasm in which could be seen an abundance of red-staining mitochondria. The nuclei were pale, rather large, and situated centrally in the cells. The larger colloid follicles showed a fair amount of papillary infolding of the walls. The size of the cells, the papillary infolding of the walls and the occurrence of numerous mitochondria were indications of hyperplasia and hyperfunction of these areas of glandular epithelium. Aside from a limited number of colloid vesicles, the bulk of the section was composed of groups of large epithelial cells without follicular formation. They represented compact areas of parenchyma composed of groups of cells separated from one another by minute septa of connective tissue.

Sections of the tumor were submitted to Dr. James Ewing who expressed the opinion that the tumor was of embryonal parathyroid type. On the other hand, after further study, it seemed more likely that we were dealing with atypical fetal thyroid gland.

Postoperatively, the patient had a moderate amount of discomfort. Swallowing soon became normal. The convalescence was uneventful, and the patient was discharged October 23, 1925, one week after operation at which time one transfixion suture was still *in situ*.

Follow-up: The child returned for examination five weeks after operation, when the single remaining transfixion suture was removed from the tongue. Her speech was distinct and definitely improved. At the base of the tongue, a small mass of tumor of firm consistency could be felt. The area of operation had healed and the patient was in good condition. Further "follow-up" examinations unfortunately were not possible.

COMMENT: The lingual thyroid nodule in the case of this young girl had produced an impediment in her speech. She seemed somewhat apathetic and was probably not as alert as a normal child of her age. The tumor was fairly large and extended from the dorsum of the tongue downward into the submandibular area. The nature of the tumor was not clear. The pathologic examination of a biopsy specimen and of the tissue removed by partial excision of the tumor revealed a structure in many respects resembling parathyroid tissue. Dr. James Ewing expressed himself as favoring this diagnosis. However, after further careful studies it seemed more likely that we were dealing with an atypical fetal thyroid gland, in fact with a so-called fetal adenomatous goiter, as frequently seen in the cervical thyroid. Such fetal types of adenoma often resemble the parathyroid in structure. If this case had been one of parathyroid origin it would seem to be the second case in the literature, the first having been reported by Asch.[6] In Asch's case tetany followed complete excision of the lingual thyroid. The post-operative course in the case just described did not afford support for or against the likelihood of the tumor being of parathyroid nature. In the first place, the excision was only partial and secondly, even though the two superior parathyroids have in a few instances been described in relation to lingual goiter the inferior parathyroids, it seems, are found in their normal cervical position and for this reason radical removal of the tumor would probably not be followed by tetany. A late "follow-up" was not possible, but five weeks after partial removal there were no evidences of tetany or hypothyroidism.

Case 3.—M. G. L., a school girl (Fig. 12), eight years of age, was first seen June 19, 1945, because of a tumor on the dorsum of the tongue. The patient was admitted to the Long Island College Hospital, October 29, 1945, and discharged November 8, 1945, after 11 days of hospitalization.

The patient's general health had been good. Tonsillectomy had been performed at the age of two. At this time the nodule on the dorsum of the tongue was not visualized. In fact it was not recognized until about two months before her present examination when, during a routine physical examination by a pediatrician, an oval mass was noted at the base of the tongue. After the lapse of a month, there had been no change in the size of the tumor. One morning, two weeks later, a spot of blood was noted on the patient's pillow. The mother became alarmed and took the child to a local hospital where the nature of the mass was not recognized, but the possibility of "thyroglossal cyst" was mentioned. The child characteristically consumed an unusually long time in mastication and deglutition and not infrequently would spend one hour to an hour and a half over a small meal. She was disinclined to swallow or talk, and her voice had a somewhat nasal quality. The appetite was poor. She was undersized for her age and seemed not to be developing normally.

FIG. 12. — Case 3: Photograph of a child, eight years of age, who presented a lingual goiter, which caused dysphagia, hesitancy of speech and a nasal quality of the voice. She was undersized, due, it appeared, to an associated mild hypothyroidism. Note the protuberant abdomen.

The patient was well-nourished but appeared undersized. There was some pallor of the skin which was of fine, thin texture. She was bright and alert, somewhat shy and slow in speech but she had done well in school. The eyes and ocular reactions were normal. The gums and dentition were in good condition. On the dorsum of the tongue, corresponding to the position of the foramen caecum, there was a sessile, rounded nodule, 2 cm. in diameter and approximated the size of a large olive. It was fairly smooth, somewhat reddened and showed several dilated, superficial blood vessels. The tumor was moderately firm and elastic. The voice was clear and there was no unusual difficulty in swallowing at the time of the examination. Her speech had a slightly nasal quality and there was a definite gulping effort when she swallowed. She masticated thoroughly and ate slowly. The heart sounds were regular in rate and rhythm. She had a noticeably protuberant abdomen. Her weight was 53 pounds and she measured 114 cm. in height. A cervical thyroid was not palpable. By indirect laryngoscopy, no evidence of laryngeal obstruction was found. The temperature was normal. The pulse averaged 85, the respirations were 22 and the systolic blood pressure was 100 mm. Hg. The basal metabolic rate was +1.4 per cent. Chemical examination of the blood showed urea nitrogen 17.2 per cent, urea 36.8 per cent and cholesterol 271 mg. per 100 cc.

Operation.—Excision of lingual thyroid—October 31, 1945: A preliminary hypodermic injection of codeine sulphate gr. 0.5 was administered. Light anesthesia was begun with chloroform, followed by ether delivered by nasal catheters. The patient was placed in a moderate Trendelenberg position with the head retracted. The jaws were spread well apart by means of a mouth gag. A stout ligature was placed through the tip of the tongue for purposes of retraction. Additional ligatures were placed in series of three through the lateral margins of the tongue. By means of traction upon these sutures, the tongue could be brought well forward, whereupon a satisfactory view of the tumor was obtained. Beginning in the region of the foramen caecum and extending backwards to the tip of the epiglottis,

an elevated bulging tumor the size of a large olive was visualized. By placing the finger behind the nodule and pressing forwards, one gained the impression that the tumor was discreet and circumscribed. Two transfixion sutures of medium size were placed through the deep substance of the tongue, one immediately anterior to the epiglottis and the second below the anterior pole of the tumor. A lenticular incision beginning at the anterior pole and extending to the posterior pole was made on either side of the tumor. The incisions were continued downwards to about the central portion of the tongue. A residuum of tissue was allowed to remain at the posterior pole. It was feared that a total resection of the tumor would remove all the thyroid tissue which the patient had. There was a surprisingly small loss of blood. The tumor had a fairly firm, elastic consistency and was a deep red color. The parenchyma was granular and fragile. In many respects it resembled normal thyroid tissue. A few cystic areas of degeneration were encountered. The superior surface of the tumor was covered by glistening mucosa in which there was a central small area, about 1 mm. in diameter, presenting a somewhat translucent, brownish appearance. A true

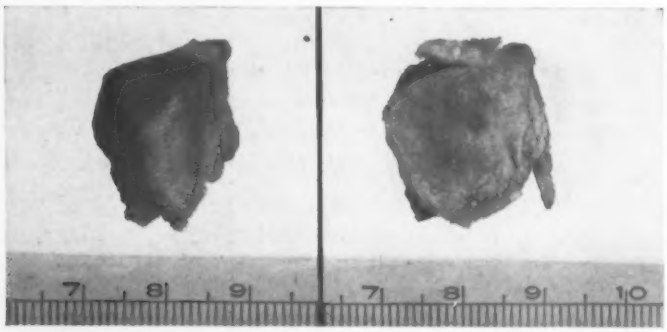


FIG. 13.—Case 3: Photographs of the gross specimen of tissue resected from a lingual thyroid tumor. On the right the mucosa covering the tumor shows a minute dark area, indicating the probable location of the foramen caecum. On the left, a lateral view of the specimen.

depression or pit to indicate the position of the foramen caecum was not visualized. Several superficial, bluish vessels were noted. The edges of the wound were then satisfactorily approximated by means of chromic catgut sutures. The deep transfixion sutures previously placed were then tied lightly across the line of incision as a precaution against postoperative bleeding. The ligature through the tip of the tongue was allowed to remain for purposes of traction in case of postoperative difficulties. The operation was well tolerated.

Pathologic Examination—Gross: The excised tumor (Fig. 13) measured 2.3 cm. in its anteroposterior diameter, 2 cm. in its greatest transverse diameter and 1.4 cm. in its vertical thickness. On the superior surface there was a central rounded area measuring 1.3 x 1.7 cm. and covered with a glistening mucosa in which several small veins were seen. This rounded area was bordered by a margin of lingual mucous membrane. The inferior margin of the tumor was limited by a zone of whitish fibrous tissue. Incision into the tumor exposed a light pink, glistening, finely lobulated, glandular tissue of uniform character which gave the appearance of normal colloid thyroid. The stroma of the tumor was sparse and there were no areas of cyst formation, degeneration or hemorrhage.

Microscopic: A sagittal section, representing the entire resected specimen was made (Fig. 14). Anteriorly and posteriorly the lingual mucous membrane was fairly thick and composed of typical stratified squamous epithelium. Over the center of the tumor the mucous membrane was thinned out in a small area which corresponded approximately to

the location of the foramen caecum. In the thin submucosa there were groups of serous and mucous glands characteristic of the tongue. Focal areas of lymphoid tissue were seen overlying the posterior portion of the nodule. Everywhere the thyroid tissue composing the nodule was sharply defined from the musculature of the tongue, but nowhere was there a limiting fibrous membrane or capsule. The posterior irregular limits of the resected specimen indicated the line of transection of the posterior pole which was allowed to remain *in situ*. The bulk of the tumor was composed of large and medium-sized acini, which contained an homogeneous pink-staining colloid and which were lined by a single row of low cuboidal or flattened, granular or vacuolated follicular cells (Fig. 15). The nuclei were rounded, oval or flat and pycnotic. Here and there were small areas of hyperplastic-appearing follicles showing papillary infolding of the lining cells. The interacinar stroma was scant throughout. The blood vessels were small and few in number and there were no areas of degeneration or hemorrhage. *Pathologic Diagnosis:* Simple colloid goiter with small areas of hyperplasia.

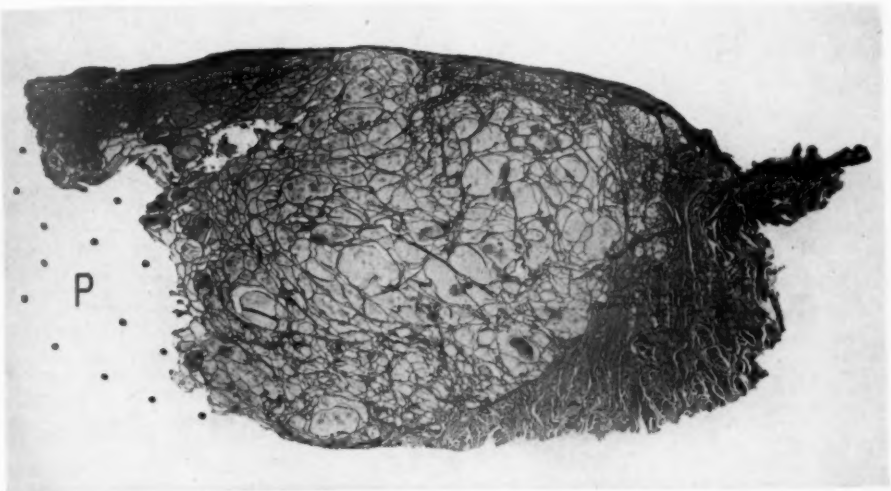


FIG. 14.—Case 3: Photomicrograph of a sagittal section of the resected specimen of lingual thyroid tumor, in the case of a girl eight years of age (Fig. 12). The structure closely resembles that of simple colloid goiter. Note the absence of encapsulation. The dotted area (P) represents the posterior pole of the nodule, which was transected and allowed to remain *in situ* to prevent postoperative myxedema. (× 4.5)

On the ninth day following operation the patient was briefly anesthetized and the sutures which had not previously sloughed out were removed, thus clearing the entire operative area. The posterior pole of the lingual nodule, which was spared, could be palpated. The patient was discharged on the 11th postoperative day, with normal temperature, pulse and respirations. Swallowing was comfortable and prompt.

Follow-up: The patient returned for examination December 1, 1945, one month after operation. There had been a gain of two pounds in weight, and she showed definite evidence of a mild hypothyroidism indicated by puffiness about the eyes, a sleepy appearance, cold hands and feet and a facial pallor. She had complained of occasional sharp pains in the muscles of the neck and legs often seen in postoperative hypothyroidism. The difficulties of deglutition had disappeared and her appetite had improved. The throat was normal in appearance, there was no swelling at the base of the tongue and the area of operation was well healed. The pulse was 84. The patient had returned to school.

It is interesting that the level of cholesterol increased from a preoperative level of 271 mg. per 100 cc. of blood to 438 mg.

Five weeks after operation, on December 8, 1945, the basal metabolic rate was minus 6 per cent. It had thus fallen 5.4 per cent below the preoperative level. In view of the mild hypothyroidism present the daily administration of one thyrothiamine tablet, containing one-half grain of thyroid extract, was prescribed.

The patient returned for further examination January 29, 1945, at which time it was stated that the former difficulties of deglutition had been practically relieved. There were

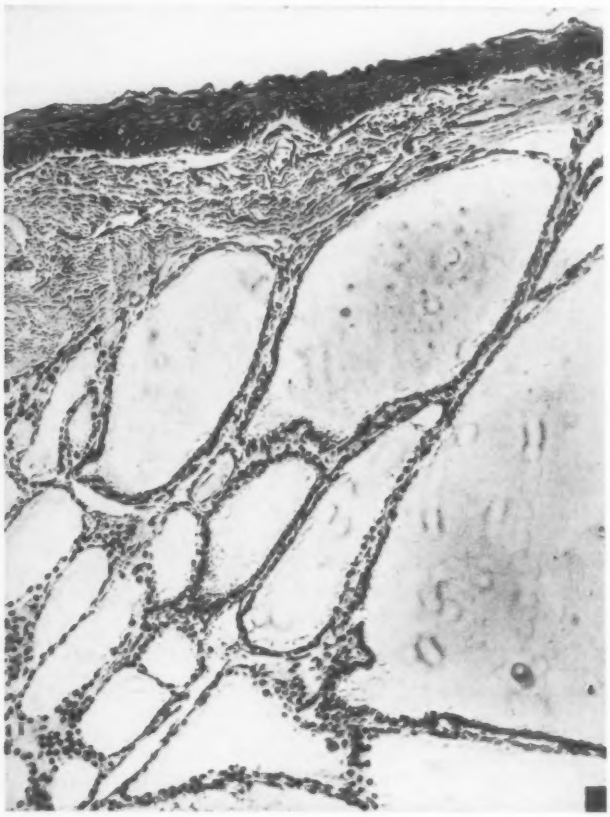


FIG. 15.—Case 3: Greater magnification, photomicrograph of section shown in Figure 14. Note the large distended colloid acini lined by a single layer of low cuboidal cells and the thin layer of mucosa covering the tumor. (× 125)

no complaints referable to the tongue and throat. Five weeks of therapy with thyroid extract gr. 0.5 daily had produced a striking change. She was more animated and alert. The slight puffiness of the face and eyelids, as well as the pains in the muscles, had disappeared and the hands and feet had become warmer. The pulse had increased from 74 to 102. Her weight was 53 pounds, 3 pounds above the preoperative weight. The continued administration of one-half grain of thyroid extract daily was advised.

On March 28, 1946, five months following operation and after three and one-half months of thyroid medication, she was in excellent condition. There had been no return of the

manifestations of hypothyroidism and the pulse was 104. The throat was normal and there was no delay in swallowing. The weight was 54 pounds. The continued daily administration of thyroid extract gr. 0.5 was advised.

During the following three months, the patient was kept in good health by the daily maintenance dose of one-half grain of thyroid extract. She was growing noticeably, and her figure was becoming more slender. There was no recurrence of the tumor. The pulse averaged 96. At the time of her last visit, September 21, 1946, she weighed 57 pounds, having gained 3.5 pounds in three months. Her height June 11th was 114 cm. and September 21st was 123 cm., an increase of 9 cm. in three and one-half months. Thyroid gr. 0.5 daily was continued.

COMMENT: The lingual nodule in this girl, eight years of age, caused difficulty in deglutition, an impediment in her speech and finally a mild hemorrhage. It was of homogeneous structure composed of a uniform hypertrophied thyroid tissue of the simple colloid type, as seen in the cervical thyroid. It could, therefore, correctly be called a simple colloid goiter. The child was undersized and showed evidences of a mild hypothyroidism. The goiter *per se* doubtless represented the only thyroid tissue which the patient possessed, for after partial excision of the tumor, the local obstructive symptoms were relieved but a definite moderate hypothyroidism with an increase in the level of blood cholesterol ensued. Excellent health was maintained with relief of all symptoms of hypothyroidism by the daily administration of one-half grain of thyroid extract. She gained in stature and appeared to develop normally. In retrospect, it would appear that this case undoubtedly might have been suitable for medical therapy such as one employs in the treatment of cervical colloid (endemic) goiter, namely, with minimal doses of iodine and adequate doses of thyroid extract. If we had known the histologic character of the lingual nodule before operation and had instituted medical treatment with thyroid extract and iodine, there is reason to believe that a satisfactory reduction in the size of the tumor could have eventually been obtained without operation. The length of time required may vary in the individual case.

Montgomery[1] reported a case in which medical therapy was instituted. However, the period of the treatment was too brief to expect more than a limited reduction in the size of the goiter as contact with the patient was lost.

DISCUSSION.—There seems to be no general agreement among embryologists as to the origin and development of the thyroid gland. The origin of the lateral thyroid lobes and the part played by the ultimobranchial bodies in their development has long been a controversial subject. It is not intended to discuss this difference of opinion in the space of this review but rather to refer to a brief recent account of the embryology of the thyroid given by Arey,[7] which is probably accepted by most students of the subject.

The main mass of the thyroid gland develops from an evagination from the ventral pharyngeal wall, which becomes the thyroid diverticulum. The latter quickly becomes a solid mass attached to the pharynx by a narrower neck. Even at four weeks, the diverticulum may be bilobed. The neck is known as the thyroglossal duct for the reason that it temporarily connects the primitive thyroid with the tongue, at the aboral border of the tuberculum impar. The thyroglossal

duct atrophies during the fifth week but its point of origin on the tongue, frequently indicated by an enlarged pit, is named the foramen caecum. As soon as the thyroglossal duct is set free, the thyroid is converted into an irregular mass of epithelial plates. Early in the seventh week, the gland becomes crescentic in shape and comes to rest in a transverse position at each side of the trachea. During the seventh week the ultimobranchial bodies, derived from the atypical fifth pharyngeal pouches, come in contact with the main thyroid primordium and fuse with it. These ultimobranchial bodies rapidly lose their original identity and are transformed into thyroid tissue. By the end of the fourth month the conversion into thyroid follicles is completed. It is generally agreed that thyroid tissue at the base of the tongue arises from the persistent median anlage or diverticulum which is derived from the ventral pharyngeal wall. This point of origin is subsequently indicated by a pit called the foramen caecum. On the other hand, some of the earlier anatomists (Keibel and Mall)[8] inclined to the view that the ultimobranchial bodies constituted functionless rudiments and did not contribute to the formation of the lateral thyroid lobes. Others (Norris)[9] felt that it was not certain whether the lateral anlage atrophies or eventually becomes transformed into permanent thyroid tissue.

It is probable that functional thyroid insufficiency is responsible for many if not most of the simple hypertrophies of lingual thyroid tissue. This view is supported by the fact that approximately two-thirds of the persons who have been reported as having a lingual thyroid hypertrophy were without a demonstrable thyroid gland in the neck. Furthermore, just as in the case of simple hypertrophies of the thyroid gland in the neck, so it is with the lingual thyroid tissue whose susceptibility to hypertrophy is very marked during the maturing periods of puberty and early adult life. The etiology of those lingual nodules, presenting many of the changes characteristic of adenomatous goiter (Cases 1 and 2) is not clear, but probably the result of factors similar to those causative in the formation of the cervical thyroid adenoma.

In his critical analysis of 144 cases of lingual thyroid nodule Montgomery[1,2] gives a detailed account of the symptoms, physical findings, pathology and treatment. It may be useful however to summarize these data and to add certain observations based on a critical study of the cases here reported. At least 90 per cent of the patients having a lingual thyroid nodule suffer from symptoms of pressure and obstruction such as dysphagia, dysphonia and dyspnea. In the three cases reported there were extreme dysphagia, choking spells (Case 1) and hemorrhage (Case 3). Less frequently reported symptoms were fulness and a feeling of tightness in the throat (Case 1). Pain was not a symptom in any of our cases. Authoritative instances of hyperthyroidism have not been reported in cases of lingual thyroid, nor was this present in our cases.

Thyroid insufficiency was reported in about 15 per cent of the cases analyzed by Montgomery, and only one of these was in a male. This finding was present in two of our patients (Cases 1 and 3). In both patients a cervical thyroid gland was not palpable. In none of the three cases was there any appreciable retardation of mental development. Our three cases were in females. This

bears out an interesting sex relationship. In the recorded cases symptoms have been described as developing during puberty and adolescence in almost half the cases, and during adolescence and early maturity in about three-quarters. In our cases symptoms began during childhood. It is probable that the factors which are operative in producing hypertrophies and pathologic alterations in the lingual thyroid tissue, are the same as those causing the well-known changes in the cervical thyroid. In the recorded cases the disturbed menstrual function was noted only in the severe degrees of thyroid insufficiency. In our adult patient (Case 1), age 30, in spite of a mild hypothyroidism menses began at the normal time. In our second case, age 12, there were definite evidences of approaching puberty. Our third case was only eight years of age. Pregnancy and occasionally menopause have been described as probable factors in causing lingual thyroid hypertrophy in some of the reported cases. In the adult female (Case 1) the hypertrophy existed before she became pregnant.

The only unusual physical characteristics of patients with lingual goiter are those associated with thyroid insufficiency, the manifestations of which are recorded in two of our cases (Cases 1 and 3). Otherwise the group, according to Montgomery, is singularly free from associated developmental anomalies.

The gross and microscopic findings in instances of lingual goiter are particularly interesting. The nodules have been described as large as a "duck egg" and the smallest represented by merely a group of thyroid acini. Our cases varied in diminishing size from that of a golf ball (Case 1) to that of a large olive (Case 3). As in our cases so in many of the recorded ones, the shape is described as globular, the surface smooth or somewhat lobulated, the color red to dark red. The surface vessels indicate a fair degree of vascularity. The cut-surface is often yellow to brownish-red, glistening and homogeneous. There are areas of colloid and areas of degeneration (Case 1) somewhat resembling myxomatous material (Case 2). These cases resemble in many ways the appearances often seen in cervical adenomatous goiter. Therefore, it would seem that the lingual thyroid is subject to the same pathologic degenerations as the normal cervical thyroid. Thyroid nodules exhibiting adenomatous changes have been stated to be greatly in the minority. However, two of our cases exhibited such changes. The majority of cases resemble more nearly the normal thyroid tissue (Case 3).

Eighty-five per cent of the lingual thyroid tumors in Montgomery's series were histologically benign. The normal type of epthelium predominated, whereas the fetal type ranked second. Several other lingual nodules of normal thyroid gland have subsequently been reported (Smith,[10] and Lemmon and Paschal[11]). Of the hypertrophies there is the simple colloid type, illustrated in our Case 3, in which the parenchyma is characterized by large acini, distended with colloid and lined by a single row of low cuboidal and flattened epithelium. This picture is the exact counterpart of the well-known cervical colloid goiter. Next in frequency are those forms produced by the embryonic or "fetal" thyroid tissue, which resembles the histologic findings seen in the fetal adenomas of the cervical thyroid (Rosedale[12] and Ray[13]). The parenchyma is characterized

by an abundance of small acini, and solid cords and groups of cells without well-defined structure (Cases 1 and 2). The colloid is usually scant in amount or entirely absent. The appearance of hyperplasia may be found in an occasional area but has not been seen as we observe it in the diffuse toxic goiter. Degenerative changes such as occur in the cervical adenomatous goiters may also be found in lingual goiters of the adenomatous type. The histologic similarity of these nodules to that of cervical adenomas has not been sufficiently emphasized At least in two of our cases (Cases 1 and 2) a distinction would be difficult to make from cervical adenomatous goiter on the basis of histology. Lastly, lymphocytic aggregates and lymphoid follicles were found in association with one of our cases (Fig. 8, Case 2). A limiting membrane or pseudo-capsule much like that seen in cervical thyroid adenomas was present in two of our cases (Cases 1 and 2). In the instance of colloid hypertrophy (Case 3) a capsule was not present in keeping with conditions found in colloid cervical goiters.

Carcinoma occurring in lingual thyroid has been reported in several authentic cases. Tyler,[14] in 1923, was the first, it appears, to report an instance of this kind. There was metastatic involvement of the lungs and retroperitoneal nodes. The second case of carcinoma was probably that reported by Ashhurst and White,[15] in 1925. In 1935, Levi and Hankins[16] reported an instance of low grade carcinoma occurring in a lingual thyroid nodule in a woman 26 years of age. They described actual invasion of the tongue as evidenced by the irregular, poorly-formed acini and the "presence of tumor cells growing in strands between the muscle cells" of the tongue. Montgomery did not regard the case as authentic and stated that the histologic picture might be merely a fetal pattern and that the intermingling of acini and muscle fibers had been observed even in benign cases. He stated, further, that the occurrence of lingual thyroid carcinoma in the female had not been proved. Wapshaw,[17] in 1942, reported the case of a lingual thyroid which he first regarded as possibly malignant on the basis of its morphologic characteristics, the active epithelial proliferation and the intermixture of cellular masses and lingual musculature. In the absence of metastases and in view of the benign postoperative course and because of the resemblance morphologically to the so-called fetal adenoma, he came to the conclusion that his case was really benign. He collected 11 cases of carcinoma from the literature, and stated that the proven cases of malignancy occurred in males and that no confirmed case had been reported in a female. There is much support, therefore, for considering lingual thyroid in the female as nonmalignant. The diagnosis of malignancy, on histologic grounds alone, is very difficult. The confirmation of metastases and the subsequent clinical course are required for a positive diagnosis. Many of the lingual thyroids resemble the fetal adenoma of the cervical thyroid. Similarly, they are capable of producing multiple types of epithelial overgrowth suggestive of malignancy. These facts account for the reports of cases of histologic malignancy in which, however, there was no involvement of the regional nodes and which ran a postoperative, clinically benign course. In view of the preceding it is well nigh impossible for the pathologist to make a final diagnosis on the findings in a biopsy *per se*. The

fetal type of glandular overgrowth, whether in the lingual or cervical thyroid, is capable of producing various types of thyroid tissue. In one instance the tissue may resemble papillary hyperplasia as seen in diffuse toxic goiter; in another, the normal gland and finally a compact cellular overgrowth without the formation of acini but with intermixture of epithelial cells and muscle fibers suggesting invasion (Cases 1 and 2). These unusual findings have led to erroneous diagnoses of malignancy. It is, therefore, essential that many areas of the entire specimen be examined before a final diagnosis is made. For example, in one of our cases (Case 2) there were large areas which, in fact, resembled parathyroid tissue and led to the presumptive diagnosis of parathyroid tumor.

It is interesting that positively identified parathyroid tissue in close association with the lingual thyroid nodule has been observed in only one instance. Several bodies which resembled the parathyroid in structure were found in the pedicle of the tumor which was composed mainly of thyroid tissue. Myxedema and tetany followed complete extirpation of the tumor (Asch).[6] Wood reported two cases of lingual thyroid tumors in which he found areas resembling parathyroid tissue. His illustrations resemble the structures not infrequently seen in lingual thyroids as well as in our Cases 2 and 3. As a matter of fact, areas resembling parathyroid tissue are not infrequently seen in fetal adenomas of the cervical thyroid. Dr. James Ewing was of the opinion that the tissue in Wood's case was probably not parathyroid but rather of fetal thyroid nature. In two of our cases there were areas in the lingual nodule (Figs. 6 and 11) which in a definite way closely resembled the structure of parathyroid. In one of these Dr. Ewing favored the diagnosis of embryonal parathyroid tissue. However, after further study we were of the opinion that we were dealing with fetal thyroid of a type often seen in cervical adenoma. In the case of a myxedematous idiot, MacCallum and Fabyan[19] found an aplastic cervical thyroid represented by mere rudiments of thyroid gland and only one pair of parathyroid glands was present. However, normal-appearing thyroid tissue was found at the base of the tongue. In a somewhat similar case of lingual thyroid and athyreosis, Ungermann[20] described the occurrence of one pair of parathyroid glands in the region of the trachea. In view of the fact that in these two cases of lingual thyroids only two parathyroid glands were found in each instance in their normal location, it is probable that the superior pair might well occur in the region of the lingual thyroid more often than heretofore supposed. This would probably explain why tetany does not occur when complete extirpation of a lingual thyroid has been performed. Presumably a cervical pair would still be functioning.

Diagnosis: The physical findings in the reported cases and in our own cases are rather characteristic. Lingual thyroid nodules have been described in order of diminishing size, as being as large as an orange and as small as a pea. In shape they are spherical, rounded or oval. The surface contour is usually smooth, occasionally irregular. The color is dusky, purple, reddish, brownish or blue. The lesions are usually median in position, at or immediately posterior

to the foramen caecum and are attached by a broad base. Some are superficial; others penetrate into the deep substance of the tongue. In consistency the nodules are hard, elastic, soft, fluctuant or cystic. The mucosal covering is usually normal, occasionally ulcerative or hemorrhagic. Incidentally, it seems that two-thirds to three-fourths of the symptom-producing lingual nodules at the base of the tongue may be without a thyroid gland in the normal location in the neck.

Differential Diagnosis: Lingual thyroid nodules are to be differentiated from adenoma, angioma, fibroma, lipoma and nonthyroid cysts, and the rare instances of malignancy such as sarcoma, lymphosarcoma and carcinoma. The actual number of benign, nonthyroid lesions at the base of the tongue is small. There were five cases of probable lingual thyroid carcinoma reported between 1910 and 1935, according to Montgomery. They were all in males over 35 years of age.

Treatment: Since the outstanding symptoms of lingual goiter are usually the result of some degree of pharyngeal and laryngeal obstruction (Cases 1, 2 and 3), resort has usually, and correctly, been had to surgical treatment. When the lesions were located on the dorsum of the tongue, partial removal by the buccal route has been the usual procedure. Briefly stated, the steps of the operation are as follows: It is desirable to have the patient under complete anesthesia, which in our cases was accomplished by means of ether administered through nasal catheters. The head is placed in the overhanging, hyperextended position. The tongue is drawn well out of the mouth, and with forward pressure upon the posterior pole of the tumor, one obtains a good view of the tumor. Deep transfixion sutures are placed below the tumor through the deep substance of the tongue. These when tied, after the excision of the tumor, adequately control the bleeding which may momentarily be brisk. Elliptical incisions are made from before backwards through the overlying mucosa. The incisions are then carried downward in wedge-shaped fashion leaving a margin of nodule on either side and a portion of tissue at the posterior pole. Complete excision, except in the rare cases of malignancy, should, naturally, never be done. Additional mucous membrane sutures give a good approximation of the margins of the wound.

The surgical approach to the lesion has been varied according to the location and extent of the lingual tumor. Extra-oral procedures have been adopted in instances where the tumor is unusually large and has extended deep into the tongue or into the submandibular space. On such occasions submental or suprahyoid incisions have been employed (Wapshaw).[17] Electrocoagulation or actual cautery has been used especially in cases of malignancy (Ashhurst and White,[15] Levi and Hankins).[16] Actual cautery is not advised in instances of lingual goiter where complete removal or destruction is to be avoided since the damage done to the residual thyroid tissue by these means cannot be accurately appraised. The same may be said regarding roentgenray and radium. Preliminary tracheotomy (Ray),[13] with or without exploration of the neck to determine the presence or absence of a normally placed thyroid gland, has been

employed. Preliminary ligation of the lingual artery has been employed in a few instances.

The most disturbing, and also the most commonly expected complication of the surgical treatment of lingual goiter is thyroid insufficiency (Ray, Wapshaw). This occurred in two of our cases (Cases 1 and 3) in which it was mild to moderate and was adequately controlled by the administration of small doses of thyroid extract. In our second case in which the diagnosis lay between atypical fetal thyroid and embryonal parathyroid tumor a satisfactory "follow-up" was not obtained and the ultimate postoperative condition was not determined. The lapse of time before the appearance of postoperative hypothyroidism could not be determined in one of our patients because of the prompt administration of one grain of thyroid extract twice daily. In Case 3, in which thyroid extract was not given in the early postoperative period, definite signs of a moderate hypothyroidism appeared within one month following excision of the thyroid nodule. The occurrence of thyroid insufficiency following lingual thyroidectomy may be as high, it has been stated (Montgomery), as 65 to 70 per cent. Transplantation of thyroid fragments has been done, in the hope of avoiding postoperative myxedema, but with unsuccessful outcome (Ray,[13] Wapshaw).[17]

Biopsy and the employment of roentgenray and radium should not be considered unless the diagnosis of lingual thyroid cannot be definitely established. Our experience with one biopsy examination was unsatisfactory (Case 2) because infection, sloughing and prolonged inflammatory reaction supervened. These factors made subsequent surgical resection difficult and unsatisfactory. In a case of lingual thyroid reported by Ray, preliminary treatment with roentgenray and radon seeds was given under the tentative diagnosis of malignant tumor of the tongue. Infection and necrosis, which complicated the subsequent surgical excision and the convalescence of the patient, ensued. The final diagnosis was benign lingual thyroid.

It appears that lingual thyroid has never been successfully treated by medical measures. These were attempted by Montgomery in a case of lingual thyroid treated with Lugol's solution. A considerable diminution in size of the tumor followed but the period of treatment was not sufficiently long to determine the ultimate result of this treatment. If we had known before operation that the lingual tumor in our patient, eight years of age (Case 3), was of simple colloid nature, it might undoubtedly have been reduced in size by the simple use of iodine and thyroid extract found to be effective in reducing the simple colloid hypertrophies of the cervical thyroid gland.

SUMMARY

1. A critical study of three cases of lingual goiter has been reported.
2. The pathologic histology of these three cases of lingual goiter has been presented, with particular emphasis on the structural similarities to adenoma of the cervical thyroid.

3. The embryology, etiology, pathology, symptomatology, diagnosis and treatment has been discussed in relation to the three cases reported, and some of the pertinent literature.

BIBLIOGRAPHY

1 Montgomery, M. L.: Lingual Thyroid: A Comprehensive Review. West. J. Surg. Obs. & Gynec., **43**, 661, 1935; **44**, 54, 122, 189, 238, 301, 373, 442, 1936.

2 *Idem:* The Lingual Thyroid: A Monograph. West. J. Surg. Obs. & Gynec., Portland, Oregon.

3 Buckman, L. T.: Lingual Thyroid. The Laryngoscope, **46**, 765, 1936; *idem:* Lingual Thyroid: Summary of Case Reports. The Laryngoscope, **46**, 888 and 936, 1936.

4 Hickman, W.: Congenital Tumor of the Base of the Tongue Pressing Down the Epiglottis on the Larynx and Causing Death by Suffocation Sixteen Hours after Birth. Tr. Path. Soc., London, **20**, 160, 1869.

5 Bernays, A. C.: The Origin of the Foramen Caecum Linguae, as Shown by an Operation on a Rare Tumor of the Root of the Tongue: A Preliminary Note. St. Louis Med. & Surg. J., **55**, 201–205, 1888.

6 Asch, R.: Die Zungenstruma, gleichzeitig ein kasuistischer Beitrag zum Myxoedem und zur Frage der postoperativen Tetanie. Deut. Ztschr. f. Chir., **130**, 593, 1914.

7 Arey, L. B.: Developmental Anatomy. 4th Ed. 211, 1941. W. B. Saunders Company, Phila. and London.

8 Keibel, F., and Mall, F. P.: Manual of Human Embryology. **2**, 462, 1912. J. B. Lippincott Company, Phila. and London.

9 Norris, E. H.: The Morphogenesis of the Follicles in the Human Thyroid Gland. Amer. Jour. Anat., **20**, 411, 1916.

10 Smith, C.: Lingual Thyroid. Arch. Otolaryng., **29**, 78, 1939.

11 Lemmon, W. T., and Paschal, G. W.: Lingual Thyroid. Amer. Jour. Surg., **52**, 82, 1941.

12 Rosedale, R. S.: Intralingual Thyroid. Ann. Otol. Rhin. & Laryn., **45**, 1009, 1936.

13 Ray, B. S.: Lingual Thyroid. Arch. Surg., **37**, 316, 1938.

14 Tyler, A. F.: Carcinoma of Lingual Thyroid with Metastases in the Lungs. Jour. of Radiol., **4**, 381, 1923.

15 Ashhurst, A. P. C., and White, C. Y.: Carcinoma in an Aberrant Thyroid at Base of Tongue. Jour. Amer. Med. Assoc., **85**, 1219, 1925.

16 Levi, L. M., and Hankins, F. D.: Carcinoma of Lingual Thyroid. Amer. Jour. of Cancer, **23**, 328, 1935.

17 Wapshaw, H.: Lingual Thyroid: A Report of a Case with Unusual Histology. Brit. Jour. Surg., **30**, 160, 1942.

18 Wood, F. C.: Thyroid and Parathyroid Tumors of the Tongue. Proc. N. Y. Path. Soc., **16**, 84, 1916.

19 MacCallum, W. G., and Fabyan, M.: On the Anatomy of a Myxoedematous Idiot. Johns Hopkins Hosp. Bull. **18**, 341, 1907.

20 Ungermann, E.: Über einen Fall von Athyreosis und vikariierender Zungenstruma. Virch. Arch., **187**, 58, 1907.

142 Jaralemon St.
Brooklyn, N. Y.

CONCERNING SURGICAL TREATMENT OF TRAUMATIC INJURY OF THE UPPER DIVISION OF THE BRACHIAL PLEXUS (ERB'S-TYPE)*

ALEXANDER LURJE, M.D.
MOSCOW, U.S.S.R.

FROM THE SURGICAL DIVISION OF BLAUGUSHIN'S HOSPITAL, MOSCOW, U. S. S. R.
DIRECTOR, PROF. F. M. LAMPERT.

IN CASES OF INJURY of the "upper primary fasciculus" of the brachial plexus, (which is formed as a result of confluence of the 5th and 6th cervical roots) the classical method of choice is direct suturing after resection of neuroma and removal of scar tissue. Foerster, Babchin and we observed restoration of the function of *m. deltoideus* and *m. biceps* 6–18 months after operation. Having performed 82 operations upon the brachial plexus we became convinced that in many cases the defect, formed after removal of neuroma and scar tissue, is so great that direct suturing—to unite the divided ends of the upper primary fasciculus (or its elements)—becomes impossible. Recourse to transplants in such cases does not appear to hold much promise. In certain cases it is possible to employ implantation into the peripheral end of the divided upper primary fasciculus of some neighboring nerve which would serve as a neurotizer. Such nerves as *n. phrenicus, n. thoracalis longus,* or one of the *nn. thoracales anterior* (a method used by Foerster, and by us) could be used for the purpose.

However, in many cases the damage may be so extensive that the above nerves cannot be employed with any hope for success. Sometimes there is a considerable difference in the dimensions of the neurotizer and of the cut-end of the upper primary fasciculus, so that it becomes doubtful whether the size of the neurotizer would be adequate to assure sufficient supply of growing fibers for the basic pathways of the peripheral end. We have made use of the neurotizers in a series of operations in which the neurotizers were implanted into the peripheral trunk of the plexus after it was isolated in the zone of injury. The remote results of such operations will be described elsewhere.

Our experience in the surgery of large destruction of single trunks of the *plexus brachialis,* led us to the conclusion that certain muscular branches of the plexus (those which could be used without impairing essentially the function of the extremity) could be profitably used as neurotizers for the functionally more important peripheral nerves, which had been traumatically severed. It seemed rational to neurotize the divided nerves as far distally from the zone of injury as possible. This is, of course, to assure optimal conditions of regeneration and, thus, to shorten the period of healing. The execution of the operation distally from the zone of trauma (and scarification) also makes the suturing, *etc.,* technically much easier.

* Translated by S. A. Komarov, M.D., Ph.D.

The operation of neurotization, when indicated by exploration, can be conveniently carried out as the concluding step of the exploratory operation. In many cases, when the exploratory operation, for some reason, has been lengthy, neurotization can be carried out as a separate second-stage. Sometimes a preliminary examination of the scars and a study of the local changes in the zone of trauma permits a purely clinical diagnosis of the impossibility of restoring any function by means of surgery in the traumatized area. In these cases it is advisable to undertake neurotization from an incision made distally from the zone of trauma. While considering such a decision, one must have in mind that very often patients will not consent to undergo a second operation after the first has not brought about any functional improvement.

In traumatic lesions of the upper primary fasciculus (so-called Erb's paralysis), there is a loss of function of *n. suprascapularis, n. axillaris* and *n. musculocutaneus,* with atrophy of the corresponding muscles.

As a result of the study of topography on 100 cadavers, we have concluded that the following nerves can be rationally used for neurotization of the above-mentioned nerves: *n. thoracalis longus, nn. thoracales anterior rami tricipitis of the n. radialis, n. thoracalis dorsalis,* and *n. subscapularis*—providing these nerves contain a sufficient number of the intact fibers. Foerster, and others, have successfully employed *n. thoracalis dorsalis* and *n. subscapularis* in cases of isolated injury of the *n. axillaris.* He also described a successful neurotization of the peripheral end of *n. musculocutaneus* with *nn. thoracales anterior.* Analogous operations are described by Vulpius and Stöffel in their handbook. It should be mentioned that these operations were used separately in cases of isolated injuries of the axillary nerve and *n. musculocutaneus,* where the defect in these nerves after revision of the zone of injury could not be repaired by direct suturing.

N. thoracalis longus is usually formed by the branches from C5, C6, and C7, which emerge from the corresponding roots at the level of the processus transversalis. The roots from C5 and C6 pass through the substance of *m. Scalenus medius.* The most massive trunk from C7 passes laterally on the anterior aspect of the middle scalene muscle. Often, the main trunk of *n. thoracalis longus,* and the structures forming it, remain uninjured when the upper primary fasciculus is completely destroyed, and in such cases this nerve can be advantageously used as a neurotizer.

N. radialis gives off its branches to *m. triceps* rather high, at the level of the tendon of *m. latissimus dorsi.* At this level, or a little lower, *rami tricipitis* can be separated, tested with inductorium and used as neurotizers after having been turned upwards.

For neurotization of the axillary nerve we prefer to use two (from 3 or 4), *rami tricipitis n. radialis,* rather than *n. thoracalis dorsalis* or *n. subscapularis,* for the following reasons: *Nn. subscapulares* receive most of their fibers from the upper primary fasciculus and, therefore, in cases of Erb's paralysis, are mostly degenerated. The use of only two of *rami tricipitis* does not entirely deprive the *m. triceps* of its innervation, while the use of *n. thoracalis dorsalis*

for neurotization would entirely deprive *m. latissimus dorsi* of its nerve supply. The cross-section of two *rami tricipitis* may not be smaller, and sometimes is even larger, than that of *n. thoracalis dorsalis,* which circumstance makes implantation convenient. However, when some difficulties are encountered in the use of *rami tricipitis, n. thoracalis dorsalis* can be used for neurotization of *n. axillaris,* especially as it receives its fibers mainly from C7 and C8. *Rami tricipitis* receive their fibers from C7, C8 and T1. *Nn. thoracalis anterior* are formed by the elements of the upper primary fasciculus and by the fibers from C7 and from the lower primary fasciculus as well.

Conclusions as to the functional adequacy and choice of the nerves to be used as neurotizers and as to the degeneration of the recipient nerves are formed from the clinical study of the state of the corresponding muscles, from the results of electrophysiologic examination performed before the operation, and, also, from the results of the stimulation with inductorium and determination of chronicity during the operation.

It should be mentioned, that if some of the fibers of the neurotizer are degenerated (the fibers from the injured plexus which find their way into the neurotizer as a result of exceedingly complex nature of the plexus) then, of course, the process of neurotization of the distal segment of the nerve—whose functional restitution is our aim—would be accomplished only by the intact fibers. In order to assure satisfactory neurotization of the recipient nerve, the intact fibers of the donor nerve should give off a considerable number of collaterals, during the process of regeneration. This is facilitated by a gentle handling, with the use of sharp instruments for cutting the nerve, and the avoidance of any tension. Being distributed evenly on the cross-section of the nerve, these intact fibers will supply the recipient nerve with a sufficient number of regenerating elements, particularly, if the diameter of the nerve donor approaches that of the nerve recipient. Incidentally, such a nerve donor, with only a part of its fibers degenerated, can show a fair functional capacity on being tested electrophysiologically. It should be remembered that the caliber of the nerve recipient, which has already undergone a process of Wallerian degeneration and atrophy, is considerably smaller than that of the corresponding normal nerve. This simplifies coaptation of the epineurium in suturing the nerve donor with nerve recipient. Experimental data of Kilvington, Kennedy, Feiss, Aird and Naffziger indicate that considerably thinner donor nerves, sutured end to end to the thicker recipient nerves, are capable of giving good neurotization of the recipient nerves, with restitution of the function, even if the ratio of the cross-sections is 1 :2 or 1 :3.

A case of neurotization with the use of *nn. thoracalis anterior, n. thoracalis longus* and *rami tricipitis* of *n. radialis* in Erb's paralysis is presented here.

Case Report: Patient N., female, age 20, was wounded, December 21, 1944, in left side of the neck, by a bomb fragment. She entered the hospital August 6, 1945. On the left side of the neck there is a large scar fixed firmly to the hardened and tender underlying tissues (Fig. 1). Roentgenologic examination reveals deformation of the *processus transversalis* of C7 and a fracture of the first rib at the neck. Physical examination

shows pronounced atrophy of the scapular muscles, deltoid muscle (Fig. 2) and biceps; complete absence of the function in the shoulder joint, except for adduction (after a passive abduction) on account of contraction of *m. pectoralis* and *m. latissimus dorsi;* complete absence of flexion in the elbow joint while extension is adequate; absence of supination; pronation adequate. Movements in the radio-carpal joint and also in the wrist and fingers are well preserved. There is anesthesia in the zone of innervation C5 and C6.

Extensive cicatrization, depth of paralysis and atrophies indicated a considerable destruction of the upper primary fasciculus and possibly also of the roots C5 and C6. These conditions made doubtful the possibility of restitution of the anatomic relations by direct suturing of the injured nerves *in situ,* and of regeneration after the operation. Predicated upon these reasons, and, also, because we did not wish to operate twice (as

FIG. 1

FIG. 2

FIGS. 1 and 2.—Preoperative. Note atrophy about shoulder girdle.

the first operation above the clavicle, in our opinion, would be lengthy and not successful) it was decided to undertake implantation of the sound neurotizers into the peripheral nerves, with the aim not to impair essentially the remaining functions of the limb.

Operation.—August 10, 1945, (Lurje): Incision from the clavicle to the borderline between the upper and middle third of the arm. *M. pectoralis major* was separated from *m. deltoideus* and from the clavicle for 5-cm., and then dissected at its insertion. Next the clavi-pectoral fascia and *m. subclavius* were dissected. In the upper corner of the wound it was not hard to find the suprascapular nerve below the clavicle, while pulling slightly the outer (secondary) fasciculus of the brachial plexus. Stimulation with inductorium revealed complete degeneration of the nerve with absence of any response from the scapular muscles. *N. thoracalis longus* was found below all the trunks of the brachial plexus. Stimulation of *n. thoracalis longus* resulted in the contraction of *m. serratus anterior.* This nerve was divided below the 2nd rib in such a manner than innervation of the upper two digitations of *m. serratus anterior* was preserved; the nerve was then implanted with three fine silk sutures into the peripheral end of *n. suprascapularis* which

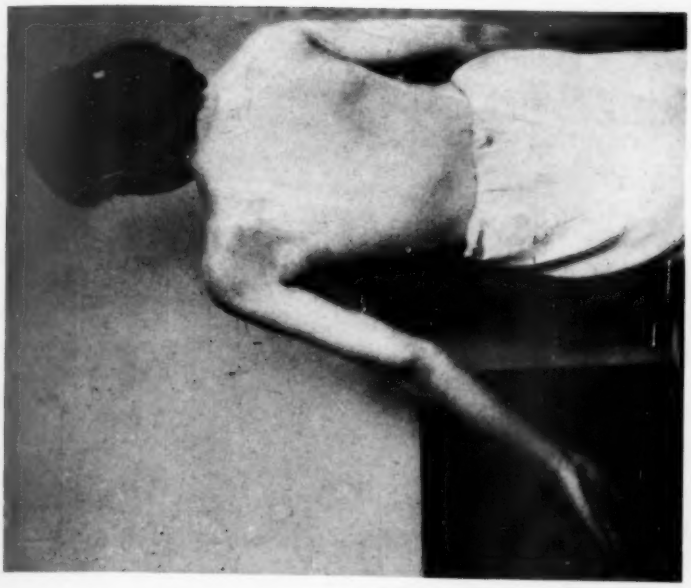


FIG. 4

FIGS. 3 and 4.—Five months postoperative. (See text.)

FIG. 3

had been divided below the clavicle. The cross-sections of both nerves were nearly the same, as the suprascapular nerve was degenerated and atrophic. In the middle part of the wound we separated two *nn. thoracalis anterior*. They emerged from the lateral secondary fasciculus of the brachial plexus (derived mainly from C7). After having verified their functional adequacy, we implanted them into the peripheral end of the previously divided (at its origin) *n. musculocutaneus*. The caliber of both *nn. thoracalis anterior* was comparable to that of *n. musculocutaneus*. It was first necessary to isolate *n. musculocutaneus* upwards from the lateral head of the median nerve with the aid of cutting instruments; the nerve was divided high, so that it would be possible to perform implantation while avoiding any tension. Implantation was made with four fine silk sutures.

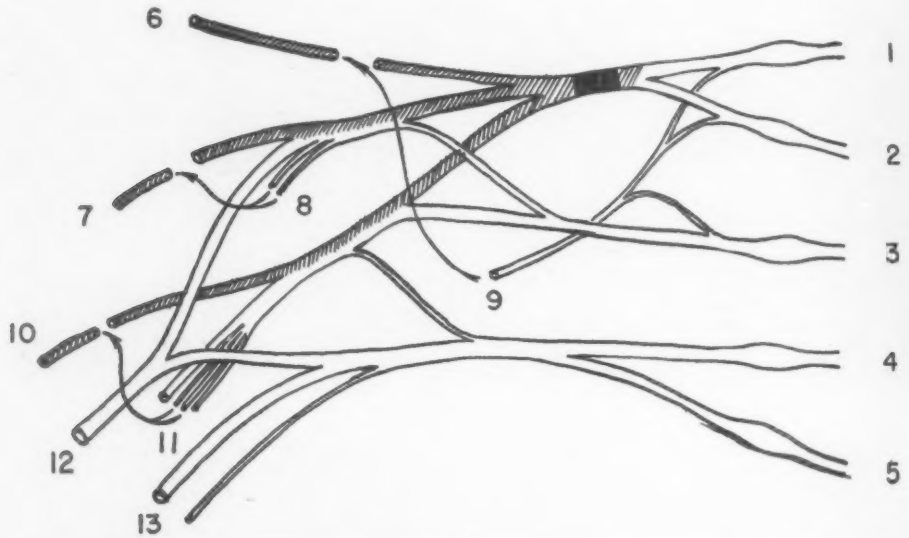


CHART 1.—1. 5th cervical nerve. 2. 6th cervical n. 3. 7th cervical n. 4. 8th cervical n. 5. 1st thoracic n. 6. Suprascapular n. 7. Musculocutanious n. 8. Anterior thoracic n. 9. Long thoracic n. 10. Axillary n. 11. Triceps rami of radial n. 12. Median n. 13. Ulnar n.

In the lower corner of the wound, we isolated three *rami tricipitis* of *n. radialis*. Two of them were divided and turned upwards and implanted into *n. axillaris*. The latter was cut on the anterior aspect of *m. subscapularis* at its origin from the posterior secondary fasciculus of the brachial plexus and then its peripheral end was turned downwards. The caliber of the nerve donor and the nerve recipient were nearly equal (Chart I).

The wound was closed in the usual way and left with drainage for 24 hours. The postoperative course was uneventful.

Already, after two months, control examination revealed a definite improvement in the functions of *mm. pectoralis* and *m. triceps* (at the time of the operation their innervation was impaired by about two-thirds). At five months, after treatment with massage and faradization, there was some restitution of movements in the elbow joint, contractions of the deltoid muscle also appeared, and atrophy began to diminish (Figs. 3 and 4).

Examination of the patient on October 10, 1946 (14 months after the operation) revealed a disappearance of atrophy of *m. deltoideus* and *m. biceps*, and a diminution of atrophy of the scapular muscles. The patient was able to contract *m. deltoideus* strongly

FIG. 5

FIG. 6

FIG. 7

FIG. 8

FIGS. 5, 6, 7 and 8.—Fourteen months postoperative. (See text.)

with abduction of the shoulder for 35°, while *m. triceps* contracts maximally at the same time (Figs. 5 and 6). Contractions of *m. supraspinatus* were quite definite. In supine position the patient was able to maintain the limb in the vertical position by virtue of the contraction of *m. deltoideus* (Fig. 7). Flexion in the elbow joint was complete with distinct contraction of *m. biceps* (Fig. 8).The strength of *m. biceps* is below that of the muscle on the right. Simultaneously with contractions of *m. biceps* there are synchronous contractions of the somewhat atrophic *mm. pectoralis;* and, similarly, contractions of *m. deltoideus* are accompanied with synchronous contractions of *m. triceps.* This phenomenon is analogous to that of synchronous contractions of the facial muscles together with contractions of muscles of the shoulder girdle, which can be observed after transplantation of *n. accessorius willisii* into *n. facialis* from half a year to a year after the operation.

Very interesting are the results of the chronaxymetric studies on our patient, which were carried out in the physiologic laboratory of the Neurochirurgical Institute (L. A. Novikova). Before the operation, *n. axillaris* and *n. musculocutaneus* gave a typical reaction of degeneration, and did not react on stimulation at a rheobase of 280v. After the operation, on October 4, 1946, *m. biceps* did not react on stimulation at a rheobase up to 200v, in spite of otherwise good function and occurrence of distinct contractions. *M. deltoideus* on the side of the injury gave chronaxy of 2.8G at a rheobase of 100v, while on the other normal side the chronaxy was 0.24G at a rheobase of 60v.

TABLE I.

April 26, 1947

Right Arm Normal			Left Arm Operation	
G	F		G	F
a<k			a>k	
2.6 mA	3	m. supraspinatus	8.0 mA	6.5
1.0 mA	3.2	m. biceps	4.6 mA	3.8
2.4 mA	3.8	m. deltoideus	5.0 mA	4.2

Absence of reaction of *m. biceps* on electrophysiologic stimulation was not surprising to us, in spite of the fact that this muscle, both as to the function and the shape, was restored much better than *m. deltoideus.* Our electrophysiologic studies on remote results of the operations on various nerves, had convinced us that in almost every case the regenerating nerve becomes passable for physiologic impulses much sooner (and more completely) than the regeneration can be established by the laboratory methods (with the use of ordinary chronaxymeters). Therefore, the clinical picture of functional restoration has a leading role in evaluating the progress of regeneration.

The subsequent electrophysiologic examination of the patient in April, 1947, established further restoration of excitability of *m. deltoideus, m. biceps* and *m. supraspinatus* both to the galvanic and faradic stimulation. These results are given in the Table I.

(Examination was carried out on a usual electrodiagnostic apparatus in the Institute of Physiotherapy, Moscow.)

The following observation is also of some interest. *M. serratus anterior sin.* gave before the operation chronaxy of 0.16G at a rheobase of 60v; 14 months after the operation the chronaxy was 0.28G at a rheobase of 65v. Both times only the lower segments of the muscle were studied. We consider that this phenomenon could be explained by the fact that *m. serratus anterior* is sometimes innervated by the intercostal nerves, as our anatomical studies, presently in progress, have shown. Roentgenologic control of the osseus apparatus of the arm—before and after operation—established some diminution in the Sudeck's atrophy of the bones.

On the basis of our results, we feel justified in recommending the use of *n. thoracalis longus, nn. thoracalis anterior, rami tricipitis* of *n. radialis* (after proper physiologic examination) for neurotization of *n. suprascapularis, n. museulocutaneus* and *n. axillaris.* We regard this combined transplantation as a typical one in treatment of Erb's paralysis, in cases where the corrective operation *in situ* above the clavicle cannot be carried out. We believe that, in cases of upper Erb's paralysis, partial loss of the function of *m. pectoralis* and *triceps* following section of two *rami tricipites* and two *nn. thoracales anterior* used for neurotization cannot make the function of the whole limb essentially worse. A part of the innervation of *m. pectoralis* and of *m. triceps* will be preserved, and, with proper exercise, the strength of these muscles can be restored, as we have seen in our patient. It is somewhat harder to evaluate the question of whether sectioning *n. thoracalis longus* is admissible. While performing neurotomy distally from emergence of the fibers to two upper indentations of *m. serratus anterior* we do not entirely deprive this muscle of its innervation. However, instead of *n. thoracalis longus, n. thoracalis posterior* can be employed for the purpose. The use of the latter nerve, according to Foerster, is already strongly indicated because exclusion of *m. latissmus dorsi,* as an antagonist, will aid restoration of the function of *m. deltoideus.*

On the basis of our experience with isolated injuries of the supraclavicular nerve, we regard its regeneration as important for the restoration of function of abduction in the shoulder joint and therefore its neurotization as desirable.

In our method of operation three physiologically important nerves: *n. suprascapularis, n. axillaris* and *n. musculocutaneus,* obtain fresh neurotizers with a good regenerative potential, and this, as our case well demonstrates, is of great importance for success in restitution of the function. In our opinion, the use of a freshly cut healthy nerve for the purpose of neurotization is a matter of great importance, since regeneration leads immediately to neurotization of the degenerated nerves. It is also important that in the zone of healthy normal tissues outside of the area of trauma, "ideal" conditions will be found for regeneration. Ordinarily, when in the case of gun shot wound, the injured nerve is sutured *in situ,* the regenerative process takes place twice. The first regeneration results in formation of a neuroma; the second regeneration takes place after the severed ends of the nerve are refreshed and sutured together, and only the latter results in neurotization. It is known, that with the passage of time after injury the capacity of axon and its cell to regenerate diminishes

(Foerster, Egorov, Chibumacher, Bondarchuk). Therefore, it is possible, that neurotization with fresh nerves, by our modification of treatment of Erb's paralysis, even when performed a considerable time after injury, will give better results than direct suturing after resection of the neuromas.

SUMMARY

In the Erb type of paralysis, with considerable destruction of the upper primary fasciculus of the brachial plexus, where a corrective operation (restorative) cannot be technically carried out *in situ* with any hope of success, neurotization of the peripheral end of *n. suprascapularis* with *n. thoracalis longus,* of the peripheral end of *n. musculocutaneus* with *n. thoracalis anterior,* and of the distal end of *n. axillaris* with *rami tricipitis* of *n. radialis* was performed. Prior to such an operation it should be established, by clinical and electrophysiologic examination, that nerve donors have sufficient potential capacity as neurotizers, and that nerve recipients are completely degenerated. Electrophysiologic examination should be repeated during the operation, and only after that the corresponding implantations can be performed. Under the above conditions, Erb's paralysis, with extensive trauma, indicates triple neurotization below the clavicle of the degenerated nerves according to the scheme presented, provided the tissues beyond the zone of cicatrization are normal.

REFERENCES

1 Aird, and H. C. Naffziger: Regeneration of Nerves after Anastomosis of Small Proximal to Larger Peripheral Nerves. Arch. of Surg., 1939.

2 Babchin, I. S.: Operative Treatment of Extensive Injuries of the Plexus Brachialis. Handbook—"Brain Tumors and Problems of Neurosurgery." Part II. Rostov. 1936. (Russian)

3 Bondarchuk.: Report at 25th Meeting of Surgeons S. S. S. R. Moscow, October 1946. (Russian)

4 Egorov, B. G.: Report at the Conference of the Surgeons of the Hospitals RSFSR. January 1946. (Russian)

5 Feiss, H. O.: On the Fusion of Nerves. Quart. J. Exper. Physiol. **5**: 1–30, 1912.

6 Foerster, O. Burke: Foerster's Handbook of Neurology Erganzumgsband, 1929.

7 Kennedy, R.: Experiments of the Restoration of Paralyzed Muscles by Means of Nerve Anastomosis. II. Anastomosis of the Nerve Supplying Limb Muscles. Phil. Tr. Roy. Soc. London S. B., **205**: 27–76, 1914. Abstr. Proc. Roy. Soc. London, S. B., **87**: 331–335, 1914.

8 Kilvington, B.: An Investigation on the Regeneration of Nerves with a View to the Surgical Treatment of Certain Paralyses. Brit. M. J., **1**: 935–940, 1905.

9 Chibumacher: Report at 25th Meeting of Surgeons S. S. S. R. Moscow, 1946. (Russian)

10 Vulpius, O., and A. Stoffel: Orthopadische Operationslehre 2 Auflage Stuttgart Euke, 1920.

Surgical Division
Blagushin's Hospital
Moscow, U. S. S. R.

OBSERVATIONS UPON PATIENTS WITH PENETRATING WOUNDS INVOLVING THE CEREBELLUM

JOHN E. WEBSTER, M.D.,* R. C. SCHNEIDER, M.D.,†
AND J. E. LOFSTROM, M.D.‡
DETROIT, MICHIGAN

AN ANALYSIS of 300 cases of penetrating cranial wounds due to metallic fragments observed at the 36th General Hospital revealed that wounds of the cerebellum were infrequent. Ten cases, an incidence of 3 per cent, were encountered. World War I reports indicate an even lower percentage of 0.54 per cent (6 cases in 1,108). In view of the variety in the types of lesions represented, illustrating the problems in management while in the Theater of Operation, these cases are briefly reviewed.

MATERIAL

The wounds were located on the left side of the cerebellum in nine of the ten patients and were caused by shell fragments in all but three. The latter were due to bullet wounds. In two cases, the dura overlying the cerebellum was not penetrated, but contused by the metallic foreign body. In three instances, the wound of entrance was located in the neck and the associated intracranial injury escaped attention. One in this latter group was treated and evacuated as a manic type of psychotic; a second (Russian POW), developed tetanus with a cerebellar abscess due to an inadequate débridement of the unrecognized wound.

One patient, who presented an acute cerebellar subdural hematoma, was successfully treated through expeditious management in the 38th Evacuation Hospital. Another presented an inflammatory complication associated with a retained metallic fragment in the posterior fossa. The removal of the fragment resulted in improvement. In two patients, tears of the lateral sinuses were serious complications at the time of the primary débridements. In each, the hemorrhage was controlled successfully by muscle stamps, one requiring three operative attempts. Severe basilar injury involving the cranial nerves and the internal carotid artery occurred in one instance.

Five of the patients were operated upon at the 36th General Hospital, the cerebellar injury having been overlooked in four of the cases. In five patients the operations were performed at Evacuation Hospitals.

GENERAL CONSIDERATIONS

A survey of the location of surviving cranial wounds, of all types, indicated that the anterior third of the skull was involved in 31 per cent of the cases; the

* Wayne University College of Medicine, Department of Surgery, Detroit, Michigan. † University Hospital, Department of Neurosurgery, Ann Arbor, Michigan. ‡ Wayne University College of Medicine and St. Mary's Hospital, Department of Radiology, Detroit, Michigan.

parietal and temporal areas (middle third) in 54 per cent, and the occipital-cerebellar area (posterior third) in 13 per cent (occiput 10 per cent, cerebellar 3 per cent). As has been recognized in cranial injury due to causes other than penetrating metallic fragments, the highest mortality is associated with injuries which involve the posterior portions of the brain, the base and the areas contiguous to the vital centers. A low incidence of survival may be one factor responsible for the infrequency of hospitalized cerebellar wounds. Other factors most probably include the protected anatomic location of the cerebellum and the adequate covering afforded by the steel helmet made available in World War II.

A wound of the cerebellum presenting the possibilities of rapid and serious complications calls for early operation. They are, thus, in most instances, the problem of the evacuation hospital neurosurgeon.

An uncomplicated wound was observed to be managed adequately by means of a unilateral curved cerebellar exploratory incision and the employment of conventional World War II methods of exploration and débridement of the wound entrance, the tract and the cerebellar lobe. The operation, in our experience, was most wisely performed under general endotracheal anesthesia to insure control of the patient's respiration at all times while in the cerebellar position. A posterior bur opening and ventricular tap prior to exploration was advantageous. A ventricular tap was seldom required following operation.

Adequate roentgenologic studies were essential in the preoperative estimation of the location and degree of bone injury and of the probable tract of the metallic fragment. The diagnosis of a suboccipital injury may depend upon the technique used to obtain roentgen films of quality. Views of the base in a mento-vertical and an occipito-vertical position were found to be advisable.

Certain problems raised in the management of the complicated wounds may be reviewed more advantageously in conjunction with the patients' briefed record. Several such summaries follow:

CASE REPORTS

Case 1.—*Acute Subdural Cerebellar Hematoma:* A patient, B. R., was wounded in action, January 2, 1944, at 0400 hours, and was reported as being unconscious for several minutes and unable to see for five minutes. He vomited twice, one and one-half hours after injury and complained of severe headache. A note of "stertorous breathing" was made at the Field Hospital shortly after injury. He was admitted to the 33rd Evacuation Hospital in light stupor at 0120 hours on January 3, 1944. There he presented nystagmus upon right and left lateral gaze; hyperactive deep tendon reflexes; bilateral Babinski reflexes associated with a 1.5-cm. wound in the left occipital area, 2 cm. posterior to the mastoid tip. Roentgen examination "revealed a 1.5 by 1.5 cm. FB situated in the occipital region just to the right of the midline and 5 cm. above the torcula." Operation was performed at 0400 hours, on January 3, 1944, by means of an inverted U-flap over the left cerebellar area. "The dura was tense and blue. The ventricle was tapped and the fluid was under extreme pressure." Before this procedure the patient's respiration fell to eight per minute. Following incision of the dura "a massive solid subdural hematoma was evacuated." The débridement was then completed. At the end of the operation the

patient was fully conscious, and the respirations had increased to 18. Neurologic examination two days later showed a persisting nystagmus, but loss of the pyramidial tract signs previously noted. The patient's recovery was uncomplicated.

Follow-up: A letter, dated March 14, 1946, stated that: "I am working and, so far, I am in pretty good shape. My mind does not grasp ideas or problems that are complicated. Seems to me that my power of concentration has been impaired. Sometimes when I lay down I get dizzy for a moment or two. I never had any convulsion."

COMMENT: The desirability of early definitive operation in the Evacuation Hospital was well-demonstrated, since further delay may well have resulted in fatality.

Case 2.—*Overlooked cerebellar wound in a patient with an intracerebellar clot:* A patient, J. C., was wounded in action on May 11, 1944, at 1130, sustaining a "penetrating wound of the neck." There was no record of the patient's activity until May 14th, when he was admitted to a Battalion Aid Station. He was evacuated from this point with the diagnosis of "exhaustion." From a neuropsychiatric clearing company the patient was further evacuated, diagnosed as a postconcussion state. He had complained of severe headache associated with vomiting.

He was admitted to the 36th General Hospital on May 18, 1944, to a closed neuropsychiatry ward in a manic state, being completely uncoöperative. A roentgenologic examination of the skull on the day of admission showed a comminuted fracture in the left occipital area, with indriven small bone fragments for a distance of 2 cm. Examination after transfer to the Neurosurgical Ward showed the patient to be alert, but disoriented, complaining of bursting headache, increased by any movement of the head. The head was held rigidly with posturing of the occiput to the left. Horizontal nystagmus was present upon left lateral gaze only. There was marked incoördination and ataxia in the left upper and lower extremities. The fundi were normal. There was an insignificant-appearing wound of the left side of the posterior aspect of the neck.

FIG. 1.—Case 2: Recent photograph of this patient which was included with his communication of May 6, 1946.

Under general anesthesia, a unilateral curved incision was made to expose the left suboccipital area. A perforation in the posterior fossa was exposed 2 cm. to the left of the midline. The cerebellum extruded through the opening. The penetrated dura was tense after removing the overlying bone. As the dural opening was enlarged there was a sudden extrusion of clots and dark blood. This release of an intracerebellar collection of approximately 40 cc. relieved all tension and the area began to pulsate. Débridement of the cerebellar lobe was then completed and the wound closed without drainage. The patient's recovery was uneventful in spite of the late débridement (9 days).

Follow-up: A communication, May 3, 1946, stated that: "I'm getting along just fine. I haven't been able to hold a job because if I do any kind of straining, I'm bothered pretty bad with headaches. I still don't have good use of my left hand. The Veteran's Administration recently cut my compensation to 50 per cent" (Fig. 1).

COMMENT: It was established in World War I that all minor-appearing wounds of the scalp be investigated for more serious underlying injury. Wounds of the neck must also be given similar consideration. It is of interest that of ten cases, in three the entrance wound was located in the posterior neck area, and all were overlooked as a locus for intracranial injury. This particular patient, fortunately, tolerated an intracerebellar clot which deserved earlier surgical treatment.

Case 3.—*Cerebellar abscess:* A patient, V. K., (Russian P. O. W.) was wounded, March 14, 1945, sustaining a penetrating wound of the left posterior aspect of the neck. He was admitted to an Evacuation Hospital six days following. A brief note described the removal of a metallic foreign body from the neck. The patient was transferred to a General Hospital, where it was recorded, March 28, 1945, that he had been irrational for 14 days, and was on that date disoriented; showed a memory defect, and complained of vertigo and diplopia. He presented bilateral papilledema, nystagmus and severe malnutrition. The patient remained apathetic, with a fever, until the 9th of April, when he developed "convulsions and became semicomatose." Nuchal rigidity and an opisthotonic posturing was noted. Roentgenologic studies of the chest showed bilateral advanced pulmonary tuberculosis.

The patient was admitted to the 36th General Hospital on the 10th of April, acutely ill, but conscious and oriented, complaining of severe headache. He presented an opisthotonus, with repeated tetanic spasms, which occurred on the slightest stimuli. A severe masseter muscle spasm was present. Examination showed two diopters of papilledema, with retinal hemorrhages; an abnormal plantar reflex in the left lower extremity; an infected wound in the left suboccipital area draining pus. The spinal fluid was under normal pressure and contained 9,000 white blood cells per cubic mm. A culture of the spinal fluid resulted in no growth of organisms. Detailed roentgenologic studies of the skull showed a comminuted fracture of the left occipital bone. Treatment with intravenous tetanus antitoxin, sodium sulfadiazine and sodium amytal was begun.

On the 11th of April, under local anesthesia, after ventricular tap and the instillation of 10,000 units of penicillin, the infected sinus in the occipital area was excised and the posterior fossa exposed through a straight incision. Extradural pus exuded through a perforation in the dura. The dura was opened and a welling-up of thick yellowish pus occurred. An abscess cavity, 3 cm. in diameter, surrounded by a thin capsule was exposed. A rubber tube was placed just to the cavity and the wound closed after the instillation of 10,000 units of penicillin. The patient improved postoperatively. The spasms were difficult to control with sodium amytal; the "lockjaw" persisted. On the 12th of April, a series of tonic convulsions were associated with apnea, cyanosis and death.

COMMENT: This patient presented a profound diseased state, including pulmonary tuberculosis, tetanus, meningitis, with a cerebellar abscess and malnutrition. The incomplete wound management resulted in tetanus, which was believed to be the direct cause of death. The opisthotonic state with tonic spasms was of interest, since late cerebellar lesions producing increased intracranial tension may result in tonic convulsions of this order. The associated trismus; the precipitation of the spasms by touching the patient or the bed and by noises; the alertness of the patient during the attacks clearly distinguished this state from that of the cerebellar tonic fit. At autopsy, the abscess was collapsed and the surrounding area showed little reaction to

infection (Fig. 2). There was neither a pressure cone at the base nor any basilar collection of exudate. Cultures of the abscess showed growth of an anaerobic spore forming organism.

Case 4.—*A cerebellar wound associated with severe basilar damage:* A patient, F. G., was wounded in action, March 19, 1945, sustaining a shell fragment wound of the left posterior aspect of the neck and the inner canthus of the eye. Superficial débridements were performed and the patient was evacuated. The record was incomplete. Upon admission to the 36th General Hospital, on March 23 the patient was acutely ill, presenting a

FIG. 2.—Case 3: Horizontal section through the removed cerebellum shows the collapsed abscess cavity on the left, measuring about 4 cm. in length.

subcutaneous emphysema of the neck and chest; moderate dyspnea and hoarseness; bilateral ecchymosis, with proptosis and a partial external ophthalmoplegia of the left eye. The left external rectus muscle was functioning. The left eye was blind, and the pupil was fixed. There was a complete left peripheral 7th nerve paralysis and bleeding from the left ear. The sensation of the left side of the face was disturbed. No other cranial nerve or focal signs were noted at this examination. The débrided wound in the neck was draining cerebrospinal fluid. Roentgenologic studies showed a fracture of the left temporal bone extending into the auditory canal and emphysema of the chest and neck, suggesting perforation of the trachea or larynx.

On the 24th of March an endotracheal anesthesia was administered with difficulty, due to an hemorrhagic and an edematous laryngeal mucous membrane. Following the tract of the wound, an exploration of the left suboccipital region was made. The floor

of the posterior fossa was comminuted and the dura overlying the cerebellum was covered with clot, but was not penetrated. The missile had coursed inferiorly along the base of the skull. By retraction of the cerebellar lobe the jugular foramen was exposed and the 9th, 10th and 11th nerves were noted to be destroyed. The jugular vein, surrounded by clotted blood was intact. What appeared to be the petrosal sinus was severed and thrombosed. Bone fragments and débris were removed. Cerebrospinal fluid was observed to be flowing from the distal side of the transverse sinus in the depths of the tract. The wound was closed without drainage. Because of the edema of the larynx and the vagal paralysis, a tracheotomy was performed before removal of the intratracheal tube.

The patient's postoperative course was complicated by bronchopneumonia and roentgen evidence of widening of the mediastinal shadow considered as being due to a mediastinitis.

A B

FIG. 3(A).—Case 4: Photography of this patient during convalescence showing the results of the cranial nerve paralyses on the left side. The tracheotomy scar is demonstrated. (B).—Case 4: The wound of entrance and the postoperative scar of the left suboccipital area is demonstrated. There is atrophy of the tropezius muscle.

A severe sulfadiazine drug reaction also occurred. Neurologic examination during convalescence showed the following cranial nerve paralyses on the left side: II, III, IV, V (sparing of the ophthalmic division), VII, VIII, IX, X, XI, XII (Figs. 3A and 3B). There were no other neurologic manifestations. The proptosis of the left eye receded. In the course of progressive improvement, a mass in the left tonsillar area was noted when the patient subsequently complained of pain and difficulty in swallowing. This was first considered to be of inflammatory origin. The mass continued to increase in size and swelling appeared at the angle of the mandible distal to the ear which began to hemorrhage. In spite of anesthesia in the 2nd and 3rd divisions of the 5th nerve, the patient complained of severe pain in the face. Aspiration of the pharyngeal mass revealed dark blood; it was nonpulsatile and no bruit could be elicited. A tiny incision into the mass resulted in brisk hemorrhage.

On June 6, 1945, an arteriogram was made of the left internal and external carotid arteries. The contrast media did not flow through the internal carotid artery although injected directly into it. Visualization of the external carotid was normal. Following the arteriogram, exploration of the great vessels was made. The internal carotid artery at three inches from the bifurcation did not pulsate and the wall was readily compressible, having lost all resiliency, yet no point of obstruction was viewed. The external carotid appeared to be normal. The internal maxillary branch was ligated. The common carotid was exteriorized beneath the skin, for the purpose of speedy ligation if necessary. At the end of five days the mass had lost its firmness and bleeding from the left ear had ceased. The patient was then evacuated (Figs. 4A and 4B).

A B

FIGS. 4(A) and (B).—Case 4: Late photographs of patient 15 months after original injury, showing the remarkable degree of improvement in appearance.

Follow-up: The patient reviewed his subsequent course in a letter on February 26, 1946. He stated, in summary, that he was evacuated to Paris to await air transportation to the States. The day before leaving he hemorrhaged from the mouth and was operated upon. After convalescence he was transferred to the Ashford General Hospital. Upon arrival he immediately underwent an operative procedure on the left side of the neck. Ten days later "blood again rushed right out of my mouth and they again operated upon my neck and told me once again I would never have another hemorrhage. Well, I did not."

The patient gained weight from 100 to 157 pounds. A "plastic operation" upon his face was not performed "as my face has straightened up almost to normal by itself." The patient is "feeling fairly well now but I can't say that I'm fine. The thing that bothers me most is the steady noise that I hear in my head which started in July, 1945. It's a ringing noise and often times it gets severe with a loud knocking sound. The left side of

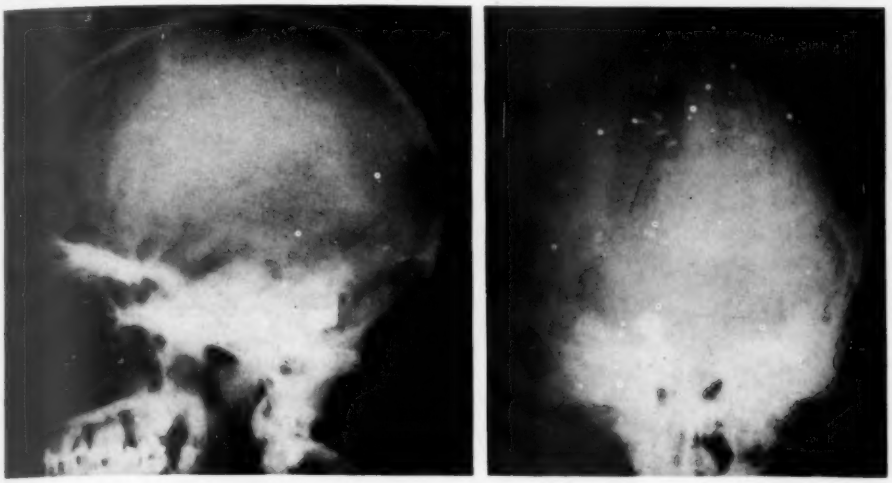
my face is still dead, also the left half of my tongue. I cannot talk very loud; I cannot holler at all and have a hard time talking on the phone. My left eye is still blind."

COMMENT: This patient survived a remarkable degree of unilateral basilar damage involving the cranial nerves and vessels and leading to serious complications. The degree of brain injury was minimal. It is of interest that the missile was never located, and if it entered the pharynx, being swallowed or expelled, the pharyngeal wound of exit was not seen. The nature of the vascular complication was not clear. The mass appeared to be an hematoma, but this was disproved upon its incision which resulted in a steady stream of venous blood. The characteristics of an aneurism were absent. When the mass palpated during exploration of the neck, its size and tension could not be influenced by compression of the carotid arteries or the jugular vein. Contrast media did not flow into the area of the mass. Explanation for the failure of the internal carotid to visualize and its anatomical appearance cannot be given.

Case 5.—*An inflammatory complication about a retained cerebellar metallic fragment:* The patient, M. G., was wounded, November 14, 1944, sustaining a penetrating wound of the right occiput, with penetration of the tentorium and the right lobe of the cerebellum. Examination at the Evacuation Hospital, November 15, 1944, showed a responsive patient, with a dysarthria and a left homonymous hemianopsia. There was conjugate deviation of the eyes to the left, with nystagmus marked upon right lateral gaze. The deep tendon reflexes were hyperactive and equal; rapid alternating movements were poorly performed; there was awkwardness upon finger to nose testing. On this date exploration was begun by means of a right occipital incision. The occipital lobe was débrided. Upon exposure of the tentorial opening a suboccipital mastoid to mastoid incision was made and the cerebellum exposed. The overlying dura was tense and blue. Ventricular puncture produced little relief in pressure. The cerebellar lobe was débrided, and troublesome hemorrhage was controlled by clipping a large vessel on the tentorial cerebellar surface. The foreign body was not removed.

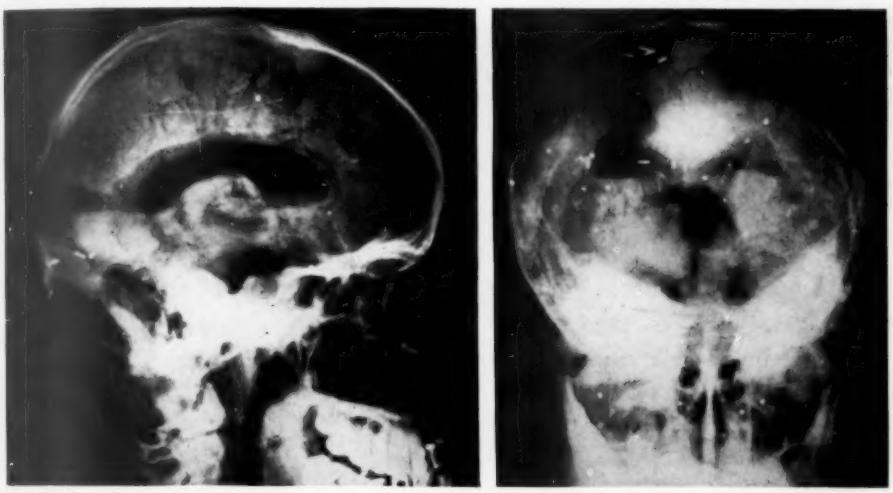
The patient was admitted to the 36th General Hospital on the 24th of November. At this date he was oriented but took little interest in his surroundings. Coarse nystagmus was present upon right lateral gaze; the fundi showed blurring of both disk margins; a left homonymous hemianopsia was present. There was weakness in the right lower extremity with more active deep tendon reflexes and bilateral Babinski signs. The cerebellar status could not be accurately evaluated since the patient performed tests poorly through apathy. The decompression site was tense. Roentgenologic study of the skull "showed a large suboccipital decompression with the operative defect extending well up in the right occipital bone as high as the lambdoid suture. There was a 1 by 1.4 cm. foreign body situated in the posterior fossa 2 cm. to the right of the midline and about 2 cm. above the floor. This placed the foreign body just above, medial and posterior to the internal acoustic meatus of the right petrosa. There were a few small loose bone fragments at the operative site near the left lower margin of the defect" (Figs. 5A and 5B). Treated by routine penicillin therapy, the patient failed to make satisfactory progress and the cerebrospinal fluid showed a pleocytosis of the 24–75 white blood cells per cubic mm. with an increased protein. Cultures of the spinal fluid at admission showed the presence of a gram-positive nonhemolytic streptococcus and a gram-positive nonhemolytic staphylococcus. Subsequent cultures after the 26th of November showed no growth of organisms. The decompression remained tense.

Reoperation was performed under endotracheal anesthesia. Pulped cerebellum was removed and a necrotic tract which extended into the vermis was débrided by aspiration



A B

FIGS. 5(A) and (B).—Case 5: Preliminary film studies on admission to the hospital, showing large occipital defect following original decompression. A large metallic fragment is imbedded in the cerebellum.



A B

FIGS. 6(A) and (B).—Case 5: Lateral and postero-anterior films following injection of air and after removal of the metallic foreign body, demonstrating the marked dilatation of the posterior portion of the body and the posterior horn of the right lateral ventricle. Considerable dilatation of the fourth ventricle following the loss of cerebellar tissue is also noted. There is some enlargement of the third ventricle, and also present is loss of air pathways over the posterior portion of the cerebrum and cerebellum.

and the foreign body lying in the end of the tract was removed. There was no pus. Culture of the tract resulted in a growth of nonhemolytic staphylococcus. An encephalogram which was made on 20th of January, prior to evacuation, showed considerable dilatation of the posterior portion of the body and the posterior horn of the right lateral ventricle. This extended almost to the surface of the cortex. There was enlargement of the third ventricle and considerable dilatation of the fourth ventricle. There was obliteration of the subarachnoid pattern over the posterior portions of the hemispheres (Figs. 6A and 6B). At discharge, the patient was ambulatory, with an ataxic gait. He was alert, oriented, having a cerebellar type of speech defect. There appeared to be severely impaired vision in the left homonymous fields. Nystagmus was present upon right and left lateral gaze; the papilledema had subsided. Severe incoördination was present in the right upper and lower extremity. The decompression was soft and the cerebrospinal fluid was normal.

Follow-up: A report from the patient, March 13, 1946, stated that he was at home on furlough. His vision was severely impaired, having what he described as "travel vision." "Side vision" only was present in the right eye. "My left eye has fair vision but it gives me a lot of trouble due to pain in the eye. I still cannot walk straight and cannot write good. Three of my brothers and myself are in the dress chicken and egg business."

COMMENT: This patient presented evidence of an unsubsiding infection as manifested by the pleocytosis of the cerebrospinal fluid; the positive cultures of the fluid and unimproving clinical status. The focus of the infection was the area of the tract about the metallic foreign body, which also cultured a pathogenic organism. The question arises whether or not penicillin therapy without reoperation may not have eventually sterilized this area. Treatment for 19 days was not effective in doing so. In our experience, large metallic fragments of this order should be removed, if accessible, at the least indication that an inflammatory complication exists. It has not been uncommon to find a localized abscess about such a foreign body, due apparently to the fact that the fragments are laden with tiny pieces of organic débris and bacteria.

RESULTS

The outcome in this group of cases was satisfactory. There was one death, resulting in a mortality of 10 per cent. This death, in a patient with an abscess of the cerebellum (Case 3), in fairness, may be attributed to tetanus rather than the cerebellar disease. The final result in the patient with severe associated cranial nerve and vascular injury (Case 4) is not fully established, and the disability is great. A third patient presented a peripheral facial palsy associated with unilateral deafness. The fourth (Case 5), has considerable visual impairment.

Six cases presented minimal neurologic defects. All were ambulatory. Cerebellar signs present upon admission improved remarkably except in the patient with the retained metallic fragment (Case 5). All the patients were returned to the Zone of Interior.

SUMMARY

1. An analysis of 300 penetrating cranial wounds showed that the cerebellum was involved in ten cases (3 per cent).

2. In three cases injury to the cerebellum was overlooked due to the location of the wounds of entrance being in the neck. Even minor appearing wounds of the posterior neck region may be associated with intracranial injury.

3. Wounds involving the cerebellum require early operation in the Evacuation Hospital, usually by means of an unilateral cerebellar incision under endotracheal anesthesia. Adequate roentgenologic studies are advantageous in the preoperative estimation of the location and the degree of injury.

4. The management of several cases of cerebellar injury which presented unusual complications were briefly reviewed.

5. The mortality in this group of patients was 10 per cent.

REFERENCE

1 The Medical Department of the U. S. Army in the World War. Vol. XI, Surgery, Part 1, p. 842.

Wayne University
1512 St. Antoine
Detroit 26, Mich.

THE SUBARACHNOID USE OF VASOCONSTRICTORS IN SPINAL ANESTHESIA*

R. J. WHITACRE, M.D., AND J. K. POTTER, M.D.
EAST CLEVELAND, OHIO

FROM THE HURON ROAD HOSPITAL, EAST CLEVELAND, OHIO

THE USE OF VASOCONSTRICTOR DRUGS has been recognized for many years as an important method of increasing the effectiveness of certain local anesthetic drugs. By delaying the rate of absorption of the anesthetic, the vasoconstrictor decreases the number of reactions and prolongs the duration of the anesthesia, thereby increasing the usefulness and safety of local and regional anesthesia. In the past, the practice of adding vasoconstrictors to the anesthetic in spinal anesthesia has met with little success, although a number of investigators[1-7] have called attention to its possible value. The present report concerns the clinical effects of epinephrine and ephedrine when they are injected into the subarachnoid space with the anesthetic drug. These two vasoconstrictors were used because they have been the drugs most frequently employed in previous investigations.

It is interesting to note that it was not long after Braun[8] first used epinephrine in local anesthesia at the beginning of the twentieth century that it was applied also to spinal anesthesia. In the years 1903 to 1905, Dönitz and Bier[9, 10, 11] reported that the addition of epinephrine to cocaine and stovaine in subarachnoid block resulted in anesthesia of greater effectiveness than did the use of these drugs alone. They believed that epinephrine both increased the length of anesthesia and decreased the toxic effects. In 1905,[12] epinephrine was also used with procaine in spinal anesthesia. For the next few years the custom of mixing a vasoconstrictor with the spinal anesthetic was common practice in some clinics. However, by the year 1915 the use of vasoconstrictor drugs in spinal anesthesia had fallen from general use. Some clinicians continued to use epinephrine with apparently good effect but the majority had become convinced that combining the spinal anesthetic with a vasoconstrictor drug was not only a needless but a dangerous practice.[13-20] In recent years several papers[21, 22] have again appeared indicating successful results with the use of epinephrine in the procaine spinal anesthesia. The most recent report was published in 1945 by Prickett, Gross and Cullen.[23] They have found that the duration of procaine anesthesia is increased 30 per cent by the addition of epinephrine to the solution.

The vasoconstrictor properties of ephedrine are less pronounced than those of epinephrine; therefore, ephedrine has not been of value in local anesthesia. It has, however, been suggested as a means of prolonging the duration

* Presented before the Section on Anesthesiology at the A. M. A. Meeting in San Francisco, in July, 1946.

of spinal anesthesia. In 1933[24] a mixture of cardiazol-ephedrine and nupercaine was used successfully. Ten years later, Romberger[22] reported that the addition of ephedrine to procaine increased the duration of anesthesia 40 to 50 per cent. It should be pointed out, however, that some experimental work[25, 26] has indicated that the subarachnoid injection of ephedrine may be accompanied by certain local or systemic reactions. Evidence has been presented that ephedrine in the subarachnoid space may cause a marked rise in blood pressure or even interfere with the function of the nerves.

Our experience with the injection of vasoconstrictor drugs into the subarachnoid space has been limited to the use of epinephrine or ephedrine with either pontocaine or nupercaine. The total number of cases in which combinations of these drugs were used has exceeded 5,000. Our principal interest in this study was to decrease the dose of the anesthetic drug. Our experience has indicated that this is an important means of increasing the margin of safety of spinal anesthesia. This view has been supported by the fact that the incidence of severe circulatory and respiratory depression has been decreased by avoiding large doses of anesthetic drugs.

The anesthetic effect of pontocaine and dextrose did not appear to be altered by the addition of epinephrine. Ephedrine, however, definitely increased the extent as well as the duration of anesthesia produced by a given dose of pontocaine. The pontocaine-dextrose-ephedrine mixture was prepared by adding sufficient 1 per cent pontocaine to a solution containing equal parts, by volume, of 10 per cent dextrose and 5 per cent ephedrine to make either a 0.20 or 0.33 per cent concentration of the anesthetic drug. Both concentrations of pontocaine were used with satisfactory results. The solution of pontocaine, dextrose and ephedrine was injected into the subarachnoid space without further dilution. It was found that compared to pontocaine-dextrose alone, approximately 30 per cent less of the anesthetic drug was needed to produce comparable anesthesia. Ephedrine apparently retards the rate of absorption of pontocaine from the spinal fluid. We observed that with ephedrine the level of anesthesia was influenced by gravity for a longer period of time after the spinal tap. Therefore, if the patient is placed in the head down position shortly after the spinal anesthetic is given, the danger of obtaining too high a level of anesthesia must always be considered. The duration of anesthesia, using 10 mg. of pontocaine or less, was increased about 20 per cent. Experience with larger doses of pontocaine was too limited for us to formulate any conclusions.

When epinephrine was added to hypobaric solutions of nupercaine, the anesthetic effect seemed to be increased. The combination of epinephrine and nupercaine used was prepared in the following manner: sufficient distilled water and 1:1000 epinephrine was added to a 1:200 solution of nupercaine, as supplied by the manufacturer, to make a 1:500 dilution of nupercaine containing a 1:25,000 concentration of epinephrine. This solution was used extensively to provide muscular relaxation for intra-abdominal operations. The hypobaric nupercaine-epinephrine solution was injected without further

dilution into the subarachnoid space with the patient in the sitting position. Following the injection the patient was allowed to sit up for one and a half to two minutes and then was placed in any desired position. All cases were immediately supplemented with a light plane of general anesthesia. With the technic described, the average dose of nupercaine necessary to obtain relaxation was 2 to 3 mg. for lower abdominal operations and 4 to 6 mg. for upper abdominal operations. In a limited number of cases small amounts of ephedrine were added to hypobaric solutions of nupercaine. Since the results did not seem to be significant, the method was discarded.

The subarachnoid injection of epinephrine and ephedrine, in the quantities and concentrations described, did not produce any systemic effects. There were no unusual respiratory or circulatory reactions. The blood pressure and pulse did not seem to be altered by the addition of these vasoconstrictors to the spinal anesthetic. It was our impression that the use of smaller doses of the anesthetic agent minimized the incidence of severe circulatory and respiratory depression. To maintain the blood pressure, an intramuscular injection of ephedrine, usually 50 mg., was routinely given prior to the spinal tap. Aside from the usual number of post-spinal headaches, there were no neurologic or other complications in this series.

Our experience supports the views of other investigators that the addition of a vasoconstrictor to the spinal anesthetic is a means of increasing and prolonging the effect of the anesthetic drug. All local anesthetics are apparently not similarly affected by the same vasoconstrictor drug. Previous workers have demonstrated that epinephrine potentiates the effect of procaine. With the particular drug combinations used in this study, epinephrine did not appreciably alter the anesthetic effect of pontocaine, but it did seem to enhance the potency of nupercaine. In contrast, ephedrine materially reduced the required dose of pontocaine, but it apparently exerted little effect when used in combination with nupercaine. Additional studies are, therefore, necessary to determine the optimum concentration of the vasoconstrictor as well as the most effective drug combinations for spinal anesthesia.

Whether the addition of vasoconstrictors to the spinal anesthetic is a real or only an apparent advantage remains to be determined by further experience. The ability to reduce the dose of the spinal anesthetic by the use of these drugs appears clinically to be of value, but it should not be assumed that proportionately less care need be taken in the administration of the anesthetic and the care of the patient.

BIBLIOGRAPHY

1 Allen, Freeman: Spinal Anesthesia. Boston M. & S. J., **163**: 715, Nov. 3, 1910.

2 Bloch, R.: L'Anesthésie a la Syncaine. Presse méd. **29**: 316, April 20, 1921.

3 Bloch, R.: L'Anesthésie Rachidienne en Chirurgie Gastrique. Paris méd., **43**: 212 March 11, 1922.

4 Deetz, E.: Erfahrungen an 360 Lumbalanästhesien mit Stovain-Adrenalin. München. med. Wchnschr., **53**: 1343, July 10, 1906.

5 Gellhorn, G.: Local and Spinal Anesthesia in Gynecology and Obstetrics. J. A. M. A., **61**: 1354, October 11, 1913.

6 Gray, H. T.: A Further Study of Spinal Anesthesia in Children and Infants. Lancet, 1: 1611, June 4, 1910.
7 Richards, O.: The Routine Use of Spinal Anesthesia. Brit. M. J., 11: 1646, December 23, 1911.
8 Braun, H.: Local Anesthesia: Its Scientific Basis and Practical Use. Translated by P. Shields, Philadelphia, Lea & Febiger, 1914, page 134.
9 Dönitz, A.: "Kokainisirung des Ruckenmarkes" unter Verwendung von Adrenalin. München med. Wchnschr., 50: 1452, August 25, 1903.
10 Bier, A., and Dönitz, A.: Rückenmarksanästhesie. München med. Wchnschr., 51: 593, April 5, 1904.
11 Bier, A.: Über den Jetzigen Stand der Rückenmarksanästhesie: Ihre Berechtigung; Ihre Vortheile und Nachtheile Gegenüber Anderen Anästhesirungsmethoden. Verhandl. d. deutsch. Gesellsch. f. Chir., 34: ii, 115–125, April 29, 1905.
12 Heineke, H. and Läwen, A.: Experimentelle Untersuchungen und Klinische Erfahrungen uber die Verwertbarkeit von Novocain fur Ortliche Anästhesie. Deutsche Ztschr. f. Chir., 80: 180, 1905.
13 Allen, C. W.: Local and Regional Anesthesia, Philadelphia. W. B. Saunders, 1914, page 432.
14 Babcock, W. W.: Spinal Anesthesia in Gynecology, Obstetrics and Abdominal Surgery. J. A. M. A., 61: 1358, October 11, 1913.
15 Barker, A. E.: Experiences with Spinal Analgesia in Reference to 2,354 Cases. Brit. M. J., 1: 597, March 16, 1912.
16 Beutner, R.: Success and Failure of Local Anesthetics. Anesth. & Analg., 22: 121, May-June, 1943.
17 Franke, M.: Über Dauerschädigungen nach Lumbalanästhesie mit Novocain-Suprarenin-Lösung. Deutsche Ztschr. f. Chir., 202: 262, May, 1927; Cited by Winograd, A. M. & Rosenbloom, H.: Spinal Anesthesia—A Review of the Literature. Illinois M. J., 59: 114–117, February, 1931.
18 Pannett, C. A.: Local Anesthesia in Upper Abdominal Surgery. Lancet, 216: 271, February 9, 1929.
19 Sebrechts, M.: Note au Sujet de la Rachianesthésie. Bull. Acad. roy. de med. de Belgique, 10: 543, September 27, 1930.
20 Sollman, T.: The Comparative Efficiency of Local Anesthetics. J. A. M. A., 70: 216, January 26, 1918.
21 Pitkin, G. P.: A Nonoxidizing Epinephrine to Prolong Spinal Anesthesia with a Subarachnoid Capacity Control. Anesth. & Analg., 19: 241, September-October, 1940; 19: 315, November-December, 1940.
22 Romberger, F. T.: Spinal Anesthesia: Practical Facts and Common Fallacies: Clinical Research on Prolonged Spinal Anesthesia using Vasoconstrictor Adjunctives. Anesth. & Analg., 22: 252 (September-October), 1943.
23 Prickett, M. D., Gross, E. G., and Cullen, S. C.: Spinal Analgesia with Solutions of Procaine and Epinephrine. Anesthesiology, 6: 469, September, 1945.
24 Jianu, A., and Moisescu, V.: Allgemeine Rhachianästhesie Mittels Perkain und Cardiazol-Ephedrin. Zentralbl. f. Chir., 60: 1166, May 20, 1933.
25 Burch, J. C., and Harrison, T. R.: The Effect of Ephedrine on the Circulation of Dogs During Spinal Anesthesia. Surg., Gynec. & Obst., 52: 953, May, 1931.
26 Schultz, F. H.: The Local Anesthetic Properties of Ephedrine Hydrochloride. Anesthesiology, 1: 69, July, 1940.

Huron Road Hospital
E. Cleveland 12, Ohio

A METHOD OF PARTITIONING LIVER PROTEINS AND ITS APPLICATION TO THE STUDY OF THE EFFECTS OF ACUTE HEMORRHAGE IN THE DOG*

WILLIAM H. FISHMAN, PH.D.
AND
HARRY H. LEVEEN, M.D.
CHICAGO, ILL.

FROM THE DEPARTMENTS OF SURGERY AND BIOCHEMISTRY, UNIVERSITY OF CHICAGO, CHICAGO, ILL.

A KNOWLEDGE OF THE PROTEIN reserve in man is of real importance in the proper medical and surgical care of the patient. The evidence in the literature,[1, 2] leads one to assume that the liver acts as a store of plasma protein. The composition of the liver protein of an individual should then reflect the state of this reserve. Accordingly, an attempt has been made to develop a method for determining proteins in liver biopsy specimens. This method has been critically tested. In addition, the effect on liver proteins of acute hemorrhage in dogs has been studied with a view to securing a basis for interpreting results on human patients.

Ideally, the individual proteins of the liver should be separated quantitatively from each other by some means which does not result in their denaturation or in the production of artefacts. In practice this would be very difficult even with the aid of complicated electrophoretic and ultracentrifugal procedures. Empirical salt-fractionation methods are more convenient for partitioning liver proteins[3] and provide results of physiological importance when careful control of all variables is maintained. The chief disadvantages of existing methods are the necessity for large specimens of liver, and the employment of long periods of dialysis and salt fractionation.

A method of estimating liver proteins suitable for use in the clinical research laboratory must be relatively convenient and reliable. In addition, only a fraction of a gram of liver would ordinarily be available. Bearing in mind these requisites, a procedure has been devised for determining liver proteins by nitrogen analysis after an initial separation into saline-soluble and saline-insoluble fractions. The former fraction may be further fractionated by strong sodium sulfite solutions. The proteins of the liver which are soluble in saline include albumin, fibrinogen, various globulins and those insoluble in saline consist mainly of connective tissue and cell membrane proteins.

METHOD FOR PARTITIONING LIVER PROTEINS

The fresh specimen of liver is made as free from blood as possible without expressing liver tissue fluid and is placed in a previously weighed glass vial,

* Aided by a grant from the Otho. S. A. Sprague Memorial Institute.

stoppered, and weighed. It is then transferred to a glass homogenizer, similar in design to the type used in preparing tissue homogenates for enzyme studies. Homogenization is carried out in the presence of 2 cc. of 0.9 per cent sodium chloride solution. After a minute or two, when intact liver tissue is no longer discernible in the mixture, the homogenate is transferred to a graduated 15 cc. centrifuge tube. Quantitative transfer is effected by homogenizing successive 2 cc. portions of saline and adding these amounts to the first homogenate. The final volume of the homogenate is made up to 6 to 12 cc. depending on the size of the specimen.

The saline homogenate is well-mixed and is centrifuged at 3000 r.p.m. for 20 minutes. After the volume of the supernatant (A) is recorded, the saline-soluble material is decanted and preserved. That portion of the homogenate insoluble in saline remaining in the centrifuge tube is suspended in 2 cc. of H_2O, centrifuged and the aqueous supernatant discarded. This washing out of the saline soluble nitrogen is repeated a second time leaving a residue (B).

The protein present in 1 cc. of supernatant A is precipitated out by adding an equal volume of 20 per cent trichloroacetic acid and is collected by centrifugation (C). Another 1 cc. of supernatant A is added to 7 cc. of 22.2 per cent sodium sulfite solution, mixed well, stoppered, and is left overnight at room temperature. Protein material flocculates out in this interval and is separated from the solution by centrifugation yielding a residue (D) and the supernatant.

To each of the precipitates obtained in steps B, C, and D is added 1 cc. of concentrated sulfuric acid solution which dissolves the residue so that it can be transferred quantitatively with the minimum amount of water to microkjeldahl digestion tubes. One cc. of supernatant A is taken for nitrogen analysis. In addition to the concentrated sulfuric acid, knifepoints of sodium sulfate, potassium persulfate, 5 drops of 5 per cent copper sulfate solution are constituents of the digestion mixture. After vigorous digestion for at least 1.5 hours or longer (if necessary to complete the digestion), the contents of the digestion tube are transferred quantitatively with rinsing to a microkjeldahl steam distillation apparatus. The ammonia is trapped in 10 cc. of 4 per cent boric acid plus 3 drops of mixed indicator (2 cc. 0.1 per cent methyl red and 10 cc. 0.1 per cent brom cresol green, both in alcoholic solution). Titration is carried out with 0.01N hydrochloric acid solution from a five milliliter microburette. Only freshly boiled distilled water may be used for rinsing the digestion tubes into the distillation apparatus. At least three reagent blanks are run with each day's determinations. The results are expressed as Gm. protein per 100 Gm. of liver.

The following terms have been employed to describe the nature of the various protein fractions. Supernatant A is considered to contain saline-soluble protein although a small fraction of the nitrogen is present in non-protein forms, "polypeptides." This amount can be estimated by the difference between the value for saline-soluble protein and trichloroacetic acid "precipitable" protein (residue C). This "precipitable" protein represents the sum of

liver albumin and globulins. By subtracting the value of residue D which contains most of the liver globulin from the figure for residue C, the liver albumin may be approximated. Residue B contains saline-insoluble protein.

RESULTS AND DISCUSSION OF METHOD

Data are presented which show the influence of the volume of 0.9 per cent saline on the relative consistency of separation of saline-insoluble from saline-

TABLE I.—*Effect of Volume of Saline on the Consistency of the Separation of Saline-Soluble and -Insoluble Material in Liver Tissue*

Wt. of Liver Specimen Mg.	Volume of Homogenate ccs.	Saline-Soluble Protein		Saline-Insoluble Protein	
		Mg.	Percentage of Liver Specimen	Mg.	Percentage of Liver Specimen
96.9	3.7	7.76	8.0	6.53	6.7
94.7	3.9	8.28	8.7	6.14	6.5
109.4	5.9	9.30	8.5	7.15	6.5
127.8	7.2	10.70	8.4	8.24	6.5
140.9	10.9	11.30	8.0	9.66	6.9
138.8	10.6	11.75	8.5	8.51	6.2
Averages and deviation			8.3±0.2		6.5±0.2

TABLE II.—*Consistency of Results of Liver Protein Partition (Biopsies taken from different lobes of the liver peripherally and centrally)*

Wt. of Specimen mg.	Saline-Soluble Protein Gm. %	Saline-Insoluble Protein Gm. %	"Precipitable" Saline-Soluble Gm. %	"Albumin-Containing" Gm. %	"Globulin-Containing" Gm. %	"Polypeptides" Gm. %
200.5	10.68	5.94	9.40	7.33	2.07	1.28
186.8	10.21	6.23	9.00	6.26	2.74	1.21
191.3	9.99	6.21	8.52	5.14	3.38	1.47
154.8	10.09	6.12	8.65	5.59	3.06	1.44
32.7	10.45	5.68	8.21	5.87	2.34	2.24
Averages and deviation	10.3±0.2	6.03±0.2	8.78±0.4	6.06±0.6	2.71±0.4	1.53±0.3

soluble material (Table I). In another experiment, all fractions of liver protein as partitioned in the method have been determined (Table II). In both of these experiments, specimens were selected at random from different lobes of the liver, both from the interior and peripheral areas.

The data show that the volume of extraction medium may vary from 5–12 cc. without materially affecting the efficiency of the separation of saline soluble and insoluble material. It is evident also from Table II that relatively consistent analyses for the various protein fractions of the liver may be obtained with the method described in this paper. This same consistency has

been found with few exceptions in the analyses reported in the dog experiments.

In preliminary experiments slightly more protein has been extracted when water was used in place of saline as the extraction medium. However, since consistent results were obtained by saline homogenization, it was decided to employ saline. It is true that the saline-soluble protein fraction is augmented slightly by the presence of blood protein left in the liver tissue spaces. One author[3] has perfused livers with saline to free them of residual blood. Since it is impossible for various reasons to employ perfusion technics in our study of liver proteins, it has been necessary to use tissue which is not blood-free. From the data, this unavoidable error does not seem to be too important.

It is important to decide what physiologic significance (if any) to attribute to the various fractions. The saline-insoluble protein represents mainly the structural protein fabric of the tissue. The saline-soluble material contains albumin, fibrinogen, various globulins, many enzymes, proteoses, polypeptides, amino acids, urea, etc. This mixture can be separated by trichloracetic acid precipitation into "precipitable" protein and "polypeptides," the latter term being used in a general sense to include the non-protein nitrogenous radicles in the mixture. The "precipitable" protein is regarded therefore as that protein in the liver cell which could function in the manner postulated by Whipple.[1] The great clinical importance which is now being attached to the plasma albumin and globulin, made it seem desirable to attempt to fractionate liver albumin and globulin so that correlations with existing knowledge might be possible. The method of Howe[4] based on the observation that globulin is selectively precipitated out by strong solutions of sodium sulfate or sodium sulfite[5] was used as a guide. Many authors have employed this method in clinical studies of protein metabolism and have drawn important conclusions from the data. However, from work reported in laboratories where the method has been critically studied[6, 7] it would appear unsound to consider the fractions obtained by salting out as containing only albumin or globulin respectively. Rather, it is evident that mixtures of albumin and globulin are separated in different proportions depending on the original albumin globulin ratio. Accordingly, in our study, we refer to the fractions thus obtained as "albumin-containing" and as "globulin-containing" with the implication that they are not systems of constant composition. There is greater variation in these fractions than in the other liver proteins which may be ascribed to the inadequacy of the salting out procedure. However, it was hoped that information of some value would be forthcoming in experiments on acute hemorrhage where extensive changes in liver protein were expected.

EXPERIMENTS ON EFFECTS OF ACUTE HEMORRHAGE IN DOGS

The liver protein partition procedure as outlined has been employed in studying the effects of acute hemorrhage on the composition of liver proteins.

In these experiments, normal dogs (7–10 kilos body wt.) were anesthetized under nembutal (25 mg. per K). Employing aseptic technic, a small incision was made in the upper abdomen, a lobe of the liver was located, a hemostatic mattress suture was placed on the liver edge and a wedge-shaped piece of tissue removed. The abdominal wound was then sutured. The femoral artery was exposed, cannulated, and 120–200 cc. of blood were allowed to escape slowly over a period of ten minutes. About three hours later, the animal was sacrificed by dividing the aorta. The liver freed of its gall-bladder was weighed. Peritoneal fluid was collected, measured, and its protein content determined. Blood proteins were determined by Kjeldahl N analyses. In each experiment at least two individual biopsy specimens were analyzed completely for liver protein at 1 hr. and 4 hrs. The results on six dogs are recorded in Table 3.

In the acute hemorrhage experiments, when the averages of the duplicate analyses are compared, four out of the six dogs (Nos. 1, 2, 3, 4) showed increases in the saline-soluble protein fraction which were due mainly to an elevation in "polypeptides." The trichloroacetic acid "precipitable" protein level was unchanged in all the animals except dog 5 in which it was lowered. In three of the animals (dogs 1, 2, 3), there were definite increases in the amount of "globulin-containing" protein, with a corresponding diminution in the "albumin-containing" fraction. Saline-insoluble protein was elevated in dogs 1, 3, 4, 5, unchanged in dog 6, but showed an apparent decrease in dog 2.

DISCUSSION

In the acute hemorrhage studies, there are a number of factors of variation which should be considered before discussing the results. In the first place, changes in tissue constituents other than the liver protein may be occurring; glycogen most certainly is disappearing from the liver, fat may increase, dehydration may occur. The presence of fluid in the peritoneal cavity results from oozing at the site of the liver excision and its quantity and protein content has been measured. The hemorrhage should be severe enough to result in a real depletion of plasma protein but should not be so extensive as to produce shock, with its accompanying disturbance to the circulation which would affect liver proteins in a manner difficult to predict. An effort has therefore been made to reduce the amount of trauma connected with the removal of the biopsy specimens and to keep the incidental blood loss down to a minimum. These considerations as well as the possible complication of infection have also led us to use a short period (4 hrs.) of experimentation which may be too short an interval of observation. It is clear also that the previous nutrition of the animal will alter the protein reserve so that the same amount of blood loss in two similar animals may have different effects on the composition of liver proteins. Accordingly, it is to be expected that the results will differ from

TABLE III.—*Liver Proteins Before and After Acute Hemorrhage*

Dog No.	Time After Initiation of Experiment (hrs.)	Wt. of Specimen Mg.	Saline-Soluble Gm. %	Saline-Insoluble Gm. %	"Precipitable" Saline-Soluble Gm.%	"Albumin-Containing" Gm. %	"Globulin-Containing" Gm. %	"Polypeptides" Gm. %
1.	1.0	153.7	9.37	6.35	7.92	2.98	4.94	1.45
		388.7	9.62	6.90	7.71	2.61	5.10	1.91
		Averages	9.45	6.62	7.81	2.79	5.02	1.68
	4.5	136.1	10.39	7.50	7.61	0.10	7.51	2.78
		85.0	10.81	7.30	7.80	0.05	7.75	3.06
		Averages	10.60	7.40	7.70	0.07	7.63	2.92
Total blood loss 217 cc. Initial and final plasma proteins respectively 4.9, 4.8, albumin 3.5, 3.4, globulin 1.6, 1.4 gr. %. Total protein loss* 12.8 Gm.								
2.	1.0	114.2	8.64	6.20	6.53	2.73	3.80	2.11
		44.3	7.88	6.81	....	....	2.39	....
		Averages	8.26	6.50	6.53	2.73	3.10	2.11
	4.5	182.9	10.62	5.32	6.77	1.95	4.82	3.85
		123.8	10.72	3.57	7.85	3.00	4.85	2.87
		Averages	10.67	4.44	7.26	2.47	4.83	3.36
Total blood loss 195 cc. Initial plasma protein 6.4, albumin 5.0, globulin 1.4 gr. % respectively. Total protein loss 14.1 Gm.								
3.	1.0	110.6	11.68	7.75	9.20	3.27	5.93	2.48
		82.1	11.85	5.77	9.34	4.98	4.36	2.51
		Averages	11.76	6.77	9.27	4.13	5.15	2.49
	4.0	89.0	12.73	8.05	9.34	2.31	7.03	3.39
		127.2	13.03	7.48	10.22	2.40	7.82	2.81
		Averages	12.88	7.75	9.76	2.35	7.42	3.10
Total blood loss 143 cc. Initial plasma protein 6.1, albumin 4.4, glob. 1.7 gr. % respectively. Total protein loss 10.0 Gm.								
4.	1.0	114.5	9.43	5.52	....	....	2.53	....
		104.8	11.03	5.84	9.39	6.71	2.68	1.64
		Averages	10.21	5.68	9.39	6.71	2.60	1.64
	4.0	91.5	11.79	7.17	9.52	6.56	2.96	2.37
		157.9	11.81	6.88	9.07	6.36	2.71	2.74
		Averages	11.80	7.02	9.30	6.46	2.83	2.56
Total blood loss 142 cc. Initial plasma protein 6.7, albumin 4.1, globulin 2.6 gr. % respectively. Total protein loss 9.6 Gm.								
5.	1.0	106.0	9.98	5.24	7.86	3.68	4.18	2.12
		115.5	9.83	6.01	7.64	4.00	3.64	2.19
		Averages	9.90	5.62	7.75	3.84	3.91	2.14
	4.0	246.3	9.43	6.93	6.81	2.64	4.17	2.62
		123.9	8.62	6.43	6.73	2.53	4.20	1.89
		Averages	9.02	6.68	6.77	2.58	4.18	2.25
Total blood loss 154 cc. Initial plasma protein 5.0, albumin 3.7, globulin 1.3 gr. % respectively. Total protein loss 7.5 Gm.								

* Total protein loss is computed from the blood loss, plasma protein and the protein content of the peritoneal fluid.

TABLE III.—*Cont'd*

Dog No.	Time After Initiation of Experiment (hrs.)	Wt. of Specimen Mg.	Saline-Soluble Gm. %	Saline-Insoluble Gm. %	"Precipitable" Saline-Soluble Gm. %	"Albumin-Containing" Gm. %	"Globulin-Containing" Gm. %	"Polypeptides" Gm. %
6.	1.0	128.7	10.61	7.13	8.12	3.90	4.22	2.49
		179.3	10.00	6.15	8.31	3.28	5.03	1.69
		Averages	10.30	6.64	8.22	3.59	4.62	2.09
	4.0	196.5	10.68	5.69	8.33	4.00	4.33	2.35
		227.8	9.80	7.16	8.23	4.93	3.30	1.57
		Averages	10.24	6.42	8.28	4.46	3.81	1.96

Total blood loss 156 cc. Initial plasma protein 5.8, albumin 3.1, globulin 2.7 gr. % respectively. Total protein loss 9.29.

animal to animal depending on how adequately the factors contributing to variation have been controlled.

It is appropriate at this point to review the status of our knowledge concerning the formation and storage of plasma protein. It is fairly well established that protein moves into the circulation to replace that lost by hemorrhage.[8, 9] It has also been shown that the liver is influenced greatly by the protein state of the individual; during periods of liberal protein intake both liver size and protein content increase most rapidly[10] and the reverse is true during fasting and during periods of low nitrogen intake.[11] On the basis of these and other considerations, Whipple and his associates have advanced the theory of a dynamic equilibrium between liver and plasma protein, with the liver normally maintaining a reserve of "labile" plasma protein available in periods of stress. This concept compels one to consider the protein in the liver as belonging to one of two discrete categories, one which is important for the life and efficient functioning of the cell, and one moiety which can leave the cell protoplasm in periods of stress, *i.e.*, after hemorrhage without affecting the activity of the cell. The best direct experimental evidence in the literature,[3, 13] indicates that no single protein in the liver functions exclusively as a storage protein and that all proteins in the liver are similarly influenced by high (or low) protein intake. Luck[13] considers "this equiproportionality of increase as indicative of a labile equilibrium *among the liver proteins* by virtue of which any tendency of a single member to accumulate is overcome by its secondary conversion into its fellow proteins." However different their viewpoints be, both Whipple and Luck envision a process by which one protein is converted into another by the regrouping of nitrogen fragments much larger in size than the amino acids, although smaller than the original protein.

The present results may now be discussed in the light of these considerations. A variety of effects have been observed from relatively minor changes in only one or two liver fractions (dog 6) to more definite alterations in most of the liver proteins (dog 1).

Importance has been attached to "precipitable" protein for the reason that it could possibly represent the protein available by one means or another, for blood protein replenishment. Does the failure of this fraction to be reduced except in one case mean that liver protein does not contribute to circulating blood proteins? Relevant to this question is the increase in saline-insoluble protein observed in four of the dogs. If this change were the result of dehydration or of the disappearance of glycogen, one would expect the "precipitable" protein to increase correspondingly. The failure for this to occur may be interpreted to mean that the liver does lose some of its protein substance after acute hemorrhage.

The elevation in "polypeptides" seems significant. It may be that the liver is more important as a site of rapid formation of plasma protein from units of protein structure (amino acids, polypeptides) carried to it from other regions of the organism. The observed increases may be the expression of an accumulation of such units.

The relative amounts of "albumin" and "globulin" in the liver varies from dog to dog. However, in three of the animals following hemorrhage, the "globulins" seem to be enhanced and the "albumin" correspondingly diminished.

If liver albumin constituted "labile" protein, then its departure into the blood stream should result in no change in "globulin" and in a decrease in both "albumin" and "precipitable" saline-soluble protein. Since "globulin" does not remain unchanged, it is difficult to point to "albumin" as a "labile" protein. If both liver albumin and globulin are being converted into plasma protein by the liver, the formation of new liver protein may take place through globulin which is later recast into albumin. This would be in accord with the concept of "interconversion of liver proteins" so that the normal partition is maintained. It may be significant that these alterations in the proportions of "albumin- and globulin-containing" fractions occur in the animals which have suffered the greatest protein loss. However, in view of the unsatisfactory state of present methods for determining albumin and globulin all that can be stated definitely is that in some of the animals the physical properties of the saline-soluble liver proteins have been so altered that more of the globulin fraction is salted-out with sodium sulfite.

Summing up the results, one can visualize changes in the liver protein partition as a result of hemorrhage which seem to be made more evident in those animals which have suffered the greatest total loss of protein. These observations offer little support for the concept of a storage protein peculiarly labile and distinct in chemical and physiologic properties from the other proteins in the cell protoplasm. On the other hand, the alterations in the relative proportion of the liver proteins are more in line with some mechanism in which active synthesis of new protein is proceeding, with the liver proteins participating to an equal extent.

Although the mechanisms involved in plasma protein formation are

extremely complicated and difficult to approach experimentally, this study does reveal the possibilities which can be explored with a simplified liver protein partition procedure. It is believed that with more uniform conditions with respect to the nutrition of the animals, a characteristic pattern of changes in the liver proteins in the great majority of animals would be demonstrated.

CONCLUSIONS

A convenient method has been devised for the partitioning of liver proteins in small specimens of liver. Two main fractions of liver tissue are first prepared, one soluble and another insoluble in physiological saline. The saline-soluble material is further fractionated into "polypeptides," "precipitable" protein, "albumin- and globulin-containing" fractions. Reproducible results have been obtained. The inadequacy of present methods of determining albumin and globulin has been pointed out.

The composition of liver protein has been studied in dogs suffering from acute hemorrhage. In some of the animals there were increases in "polypeptides," "globulin-containing," and saline-insoluble protein. In most of the dogs, the concentration of protein soluble in saline but precipitable by trichloroacetic acid was little affected by hemorrhage. However, these observations along with other findings may be interpreted to suggest that the liver has lost some of its protein. These results have been discussed in connection with the problem of the formation and storage of plasma protein in the body.

We would like to express our sincere appreciation to Dr. Dallas B. Phemister for the interest and support he has given this investigation. We are indebted to Mrs. Evelyn Gordon for her careful technical assistance.

REFERENCES

1 Madden, Sidney C., and George H. Whipple: Plasma Proteins: Their Source, Production, and Utilization. Physiol. Rev., **20**: 194–217, 1940.

2 Whipple, G. H., and S. C. Madden: Hemoglobin, Plasma Protein and Cell Protein. Medicine, **23**: 215–224, 1944.

3 Luck, James Murray: Liver Proteins 1. The Question of Protein Storage. J. Biol. Chem., **115**: 491–510, Sept. 1936.

4 Howe, Paul E.: The Use of Sodium Sulfate as the Globulin Precipitant in the Determination of Proteins in Blood. J. Biol. Chem., **49**: 93–118, 1921.

5 Campbell, W. R., and M. I. Hanna: The Albumins, Globulins and Fibrinogens of Serum and Plasma. J. Biol. Chem., **119**: 15, 1937.

6 Gray, Seymour J., and E. S. Guzman Barron: The Electrophoretic Analyses of the Serum Proteins in Diseases of the Liver. J. Clin. Investigation, **22**: 191–200, 1943.

7 Majoor, C. L. H.: The Possibility of Detecting Individual Proteins in Blood Serum by Differentiation of Solubility Curves in Concentrated Sodium Sulfate Solutions. Yale J. Biol. and Med., **18**: 419–441, 1946.

8 Stead, E. A.: Physiological Adjustments of Normal Subjects to Sudden Loss of Blood. J. Clin. Investigation, **19**: 776, 1940.

9 Wallace, J., and E. P. Sharpey-Schafer. Blood Changes Following Controlled Hemorrhage in Man. Lancet, **2**: 393–5, 1941.

10 Beattie, J., and H. B. Collard: Plasma Protein Storage. Brit. M. J., **2**: 507–511, 1942.

11 Addis, T., L. J. Poo and W. Lew: The Quantities of Protein Lost by the Various Organs and Tissues of the Body During a Fast. J. Biol. Chem., **115**: 111–116, 1936.

12 Addis, T., L. J. Poo and W. Lew: The Rate of Protein Formation in the Organs and Tissues of the Body I. After Casein Refeeding. J. Biol. Chem., **116**: 343–352, 1936.

13 Lee, William C., and Howard B. Lewis: The Effect of Fasting, Refeeding, and of Variations in the Cystine Content of the Diet on the Composition of the Tissue Proteins of the White Rat. J. Biol. Chem., **107**: 649–659, 1934.

14 Luck, J. Murray: The Liver Proteins. Perspectives in Biochemistry, p. 215, London, Cambridge University Press, 1939.

950 E. 59th St.
Chicago 37, Ill.

BLOOD AND LIVER PROTEINS IN SURGICAL PATIENTS AS RELATED TO PROTEIN DEPLETION*

HARRY H. LEVEEN, M.D.**
AND
WILLIAM H. FISHMAN, PH.D.
CHICAGO, ILL.

FROM THE DEPARTMENTS OF SURGERY AND BIOCHEMISTRY, UNIVERSITY OF CHICAGO, CHICAGO, ILL.

IN RECENT YEARS, the metabolism of protein has assumed an importance for the surgeon as great as any other subject. Operative mortality for gastrectomy has been shown to be directly proportional to preoperative weight loss.[1] Resistance to infection decreases as depletion of proteins proceeds.[2] Proper wound healing depends on adequate protein nutrition.[3] Gastro-intestinal motility decreases with hypoproteinemia at times simulating adynamic ileus.[4] A decrease in liver fat is effected by the administration of lipotropic proteins and amino acids.[5] Edema of anastomotic wounds, and abdominal wall wounds occurs in protein deficient states.[6] Postoperative asthenia is stated to respond to protein feedings.[7] Urinary suppression occasionally results from hypoproteinemia.[8] Abnormal losses of nitrogen occur after trauma.[9, 10]

The above factors have focused attention on the relationship of blood proteins to tissue proteins. Experiments on animals with chronic protein depletion have shown that a decrement in the plasma albumin of 1 Gm. per cent reflects a loss in the tissues of 30 Gm. per cent.[11] In humans, a low plasma protein value such as might result from an acute loss does not necessarily indicate that the tissues are depleted of protein. Peters states that the only absolute criterion of protein depletion is the establishment of a positive nitrogen balance. The inability to establish such a balance does not, however, signify that depletion has not occurred.[12] Studies on tissue proteins have not lent themselves to direct analysis as in the case of blood proteins, and evidence has been secured in the main by inference from nitrogen balance studies. Low plasma protein values indicate a need for protein, but one cannot ordinarily appraise the significance of such values without some information as to the relation of low plasma protein values to tissue protein reserves.

In the experimental animal and in humans loss of plasma protein by hemorrhage or plasmapheresis or acute fasting, is at first rapidly restored without additional protein feeding.[13, 14, 15] This and other evidence has led to the concept that there are available labile stores of preformed protein which the body can call upon in case of need. Additional evidence for such a depot is afforded by repletion experiments with plasma which do not lead to hyper-

* Aided by a grant from the Otho S. A. Sprague Memorial Institute.

** Present address, Department of Surgery, New York University College of Medicine.

proteinemia. The work of Whipple[15] has indicated that a major depot for these "labile" protein reserves is in the liver.

Let us consider two storehouses for protein. One the liver protein, the other the total circulating protein. What are the effects of depletion upon these reservoirs? If the protein reserves mirror the concentration of plasma protein, isolated plasma protein determinations would take on added significance as a measure of protein depletion.

It is the purpose of this study to supply direct evidence so that the effects of protein deprivation upon blood and tissues can be correlated. Blood uric acid level has been reported to be a good index of the degree of protein depletion in surgical patients.[16] Its use as a criterion has been investigated as part of our study.

METHOD

Liver biopsies for protein determination were obtained either by puncture through the abdominal wall with a Silverman biopsy needle,[17] or in most cases at the time of operation when a wedge shaped segment was removed from a non-fibrosed area on the liver surface. Plasma protein values were determined immediately before liver biopsies were obtained by either method. Specimens secured during celiotomy were always taken at the beginning of the operation. Plasma volume was determined immediately before surgery using Evans blue dye method.[18]

Liver proteins were determined as described previously[19] on 14 patients of whom four can be considered hypoproteinemic by the usual standards. The clinical diagnosis, preoperative weight loss, blood proteins, plasma volume, and liver proteins are represented in Tables I and II.

RESULTS

The Relation of Hypoproteinemia to Total Circulating Protein. Blood volume is poorly correlated with body weight, being more closely related to surface area.[20] Hypoproteinemic patients were found to have levels for total circulating protein per square meter of surface area (determined according to the method of Meeh's[21]) slightly lower than normals. (Fig. 1, Table II). The graph illustrates that there is a definite tendency for total circulating proteins per unit surface area to increase with an elevation in the total protein concentration of the serum, but the effect is by no means constant and individual values vary widely. It can be said that the protein reservoir in the form of circulating proteins is by no means uniform and the magnitude of this reservoir cannot be appraised by simple blood protein concentrations. The average total circulating protein per sq. meter of surface area in those cases having total proteins of 6.5 Gm. per cent or more was 120 ± 15 Gm. per square meter of surface area. When the total protein was less than 6.5 Gm. per cent this value dropped to an average of 115; and when less than 6.0 Gm., an average of only 72 was found.

In one patient (No. 16 in Table III) an opportunity presented itself to study the effect of chronic depletion on total circulating protein. This patient

TABLE I.—*Clinical Diagnosis—Wt. Loss and Blood Protein Studies*

Patient Number	Clinical Diagnosis	Pre. Op. Wt. Loss in lbs.	Gm. % Blood Total Protein	Plasma Volume in cc.	Grams Total Circulating Protein	Grams Total Circulating Protein Per Sq. M. Surface Area
1	Ca stomach	26	5.75	3217	185	138
2	Ca tail pancreas	10	6.64	3040	202	121
3	Ca esophagus	40	5.74	1020	58.5	47.1
4	Ca stomach	5	6.64	N.D.	N.D.	N.D.
9	Ca stomach	15	6.26	3149	197	150
10	Ca esophagus	12	7.78	3127	244	140
11	Ca pancreas	30	6.53	2912	190	109
12	Colostomy closure	30	6.58	1360	89.5	81.4
13	Cardiospasm	0	6.70	2440	164	111
15	Hemolytic Anemia	15	6.16	4234	261	179
17	Ca stomach	50	4.95	2544	126	102
18	Ca stomach	24	6.14	3307	203	117
19	Ca stomach	0	6.02	1737	105	65.2
20	Ca colon	0	6.54	N.D.	N.D.	N.D.
22	Ca stomach	20	5.52	3523	195	122
23	Normal	0	7.26	2538	184	116
24	Normal	0	7.21	2988	216	136
25	Normal	0	7.32	2816	206	122
26	Normal	0	7.68	3042	234	116
27	Normal	0	7.57	3014	228	132
28	Gastric ulcer	18	7.17	2106	151	96.3
29	Portal hypertension	0	7.16	3324	238	161

TABLE II.—*Blood and Liver Protein Determinations of Patients Represented in Table I*

	Blood Proteins (Gm. %)			Liver Proteins (Gm./100 Gm. Liver)								
				Saline Soluble								
Patient Number	Total Protein	Albumin	Globulin	Total Precipitable	Albumin	Globulin	Saline Insoluble	Ratio of Precip. Saline Soluble to Insol.	Total Sol. Nitrogen Expressed as Protein	Blood Liver Protein Ratio	Liver A/G Ratio	Blood A/G Ratio
1 pre-op	5.75	4.57	1.18	8.73	5.12	3.61	7.89	1.10	10.52	.659	1.42	3.86
1A op.	6.04	4.33	1.71	10.01	5.44	4.57	4.36	2.30	12.18	.603	1.19	2.53
2	6.64	4.32	2.32	9.20*	4.03	5.17	N.D.	N.D.	11.22	.825*	.780	1.86
4	6.64	4.27	3.27	10.36	N.D.	N.D.	7.25	1.43	12.41	.641	N.D.	N.D.
9	6.26	4.35	1.91	9.72*	5.15	4.57	6.37	1.52	11.78	.646*	1.12	2.28
10	7.78	4.24	3.54	9.43*	3.54	5.89	5.72	1.65	11.43	.825*	.600	1.20
11	6.53	4.96	1.57	9.83	6.92	2.91	5.79	1.70	12.98	.665	2.38	3.16
15	6.16	4.84	1.32	10.76	5.23	5.53	8.08	1.33	13.22	.573	.947	3.67
17	4.95	2.61	2.28	9.12	4.76	5.36	5.25	1.73	11.95	.543	.889	1.90
18	6.14	3.74	2.40	8.67	4.72	3.95	6.63	1.31	9.63	.707	1.19	1.56
19	6.02	4.36	1.66	10.42	6.40	4.02	8.93	1.17	12.00	.578	1.59	2.63
20	6.54	4.54	2.00	9.70	4.17	5.53	7.65	1.27	11.47	.675	.754	2.27
22	5.52	3.81	1.71	13.11	N.D.	N.D.	7.53	1.74	14.75	.421	N.D.	N.D.
28	7.17	N.D.	N.D.	12.98	7.85	5.13	10.20	1.27	15.45	.552	N.D.	N.D.
29	7.16	4.14	3.02	9.87	6.56	3.31	7.91	1.25	12.86	.725	1.98	1.37

Determinations of blood proteins expressed in Gm. per 100 cc.
Determination of liver proteins expressed in Gm. per 100 Gm. of liver.
* Result estimated from saline soluble nitrogen albumin fraction and globulin fraction.

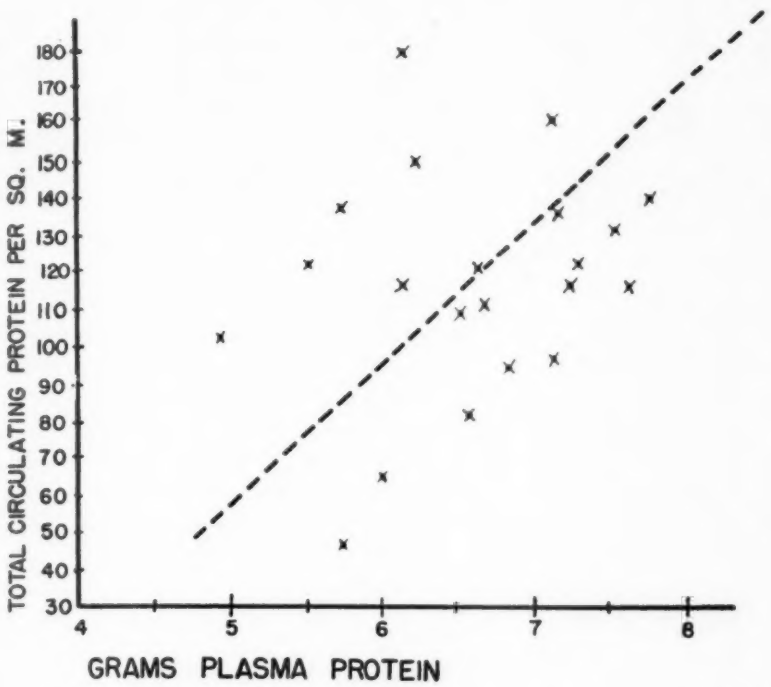


FIG. 1.—The relationship between plasma protein and total circulating protein per square meter of surface area is shown. The values for total circulating protein per Sq. M. surface area tends to rise with increasing plasma protein concentrations as is indicated by the dotted line.

TABLE III.—*Clinical Diagnosis, Weight Loss, Blood Protein and Uric Acid Concentrations in Patients with Hypoproteinemia*

Patient's No.	Diagnosis	Wt. Loss in Pounds	Total Protein Gm. %	Blood Uric Acid Mg. %
1	Ca of stomach	26.5	5.75	3.65
3	Ca of esophagus cardia	40 (9 mos.)	5.74	2.38
5	Cirrhosis and G. B. dis.	20 (3 mos.)	5.60	3.24
16	Postgastric Ca resection. Subphrenic abscess	Marked loss in hosp.	5.26	2.99
*17	Extensive Ca of stomach. Inoperable	50 (1 yr.)	4.95	3.54
22	Ca of stomach	30 (30 mos.)	5.52	7.12
**30	Ca of stomach	52 (6 mos.)	5.76	4.02

* 24 hour uric acid Excretion 215.2 Mg. ** 24 hour uric acid excretion 169.0 Mg.

had a subphrenic abscess and an internal pancreatic fistula following an extensive resection for carcinoma of the cardiac end of the stomach involving the esophagus and pancreas. The blood protein concentration fell from 6.26 to 5.26. The plasma volume decreased from 3,149 to 2,670. These circumstances effected a drop in total circulating protein from 197 Gm. to 140 Gm.

Relationship Between Blood and Liver Total Protein Concentration.—Figure 2 illustrates the relationship of blood proteins to total precipitable saline soluble protein of the liver. Again wide individual variations occur but

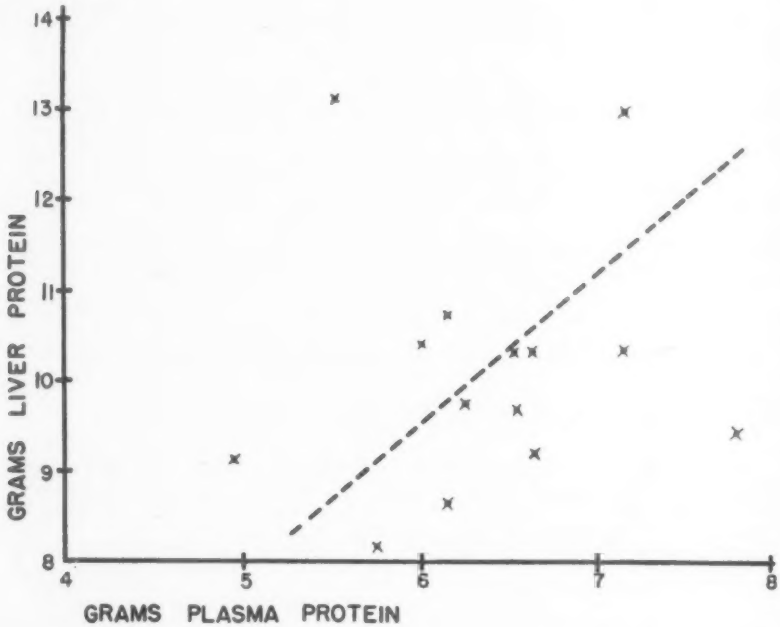


FIG. 2.—The relationship between total precipitable liver protein and plasma protein concentration is illustrated. With one exception, the liver protein concentration appears to increase with augmentation of plasma protein. This trend is designated by an interrupted line.

there is a trend toward liver protein accumulating with increasing plasma protein concentration. The normal value of total precipitable saline soluble liver proteins is in the range of 10.5 Gm. per cent. If one examines the ratio of liver protein concentration to blood protein concentration, values occur between .42 and .72 with the low ratios in the hypoproteinemic group. (Table II.) This finding may possibly indicate that liver proteins are less subject to variation than blood proteins.

Liver and Blood Albumin and Globulin Fractions. As pointed out in the previous paper,[19] serious criticisms are indicated in the use of Howe's separation of albumin and globulin by salting out whether blood plasma or tissue preparations are used. Accordingly, these data must be interpreted with caution.

The albumin-containing fraction of the liver was not significantly lower in hypoproteinemic patients (Table II). Liver globulin-containing fractions are much higher than plasma causing a reduction of liver A/G ratios as compared to blood A/G ratios. In only one instance was a liver A/G ratio greater than 2.0 found. Although there is great variation in individual results, it appears from Figure 3 that there is a direct relationship between changes in the blood albumin globulin ratio and that of the liver.

Saline Insoluble Liver Protein. The saline insoluble proteins of the liver represent the protein structural framework of the liver and as such cannot be considered available immediately for metabolic use under ordinary conditions. This fraction is of basic importance since it provides a yardstick by which changes in the concentration of soluble protein may be considered absolute or relative. For instance, an increase in liver fat will lower the concentration of saline soluble liver protein even though the total amount of this protein is unchanged. By the same token, the concentration of the insoluble protein will diminish with an increase in fat. Nevertheless, the concentration of soluble protein per unit of structural protein will remain constant even though fat, glycogen and other substances change their individual concentrations. The establishment of a normal value for saline insoluble liver protein is of great importance in the interpretation of results. The average value for saline insoluble liver protein in those patients who were normal or in a good state of nutrition was 7.46 Gm. per cent ± 1.01 (Table I). There were no significant differences noted in protein depleted states.

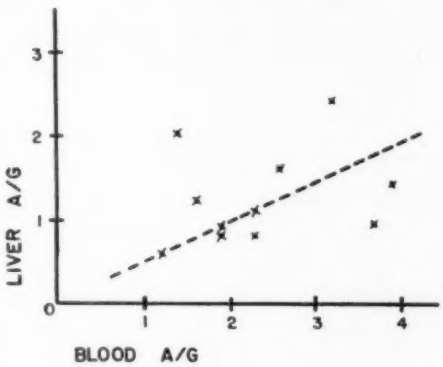


FIG. 3.—The blood A/G Ratio is plotted against the liver A/G Ratio. Except for a few results, variations in plasma protein composition seem to mirror similar changes in the saline soluble liver proteins. This tendency is represented by a broken line.

Ratio of Precipitable Saline Soluble to Saline Insoluble Liver Protein. This ratio is really the amount of precipitable soluble protein per unit protein structural mass, as was previously explained. If the liver is a storehouse for labile protein this ratio should be inconstant and fluctuate widely depending upon the amount of protein being stored. It will also be independent of the degree of hydration, fat content, and glycogen content. The ratios as expressed in Table II are all quite constant and lie between 1.11 and 1.73; a fact which diminishes the possibility of any large store of preformed plasma protein in the liver. As evidence for the validity of the statement that the ratio of precipitable saline soluble liver protein to saline insoluble does not change even with changes in fat concentration, one patient with advanced lipoid dystrophy was studied. This patient even had an extensive enlargement of the liver and spleen. The values for precipitable saline soluble and insoluble proteins in

this case were only 6.50 Gm. per cent and 5.37 Gm. per cent respectively. The ratio was 1.21 which is in the region observed for normal patients. (Case not included in tables).

EFFECT OF PLASMA TRANSFUSION ON LIVER PROTEINS

One patient with carcinoma of stomach (No. 1 in tables) was seen after a period of active bleeding and complete pyloric obstruction. He had lost 26 pounds in a period of 2 months. His plasma proteins were 5.74. He was given 3300 cc. of plasma and 1000 cc. of blood over a period of 4 days preoperatively. The first liver biopsy was obtained by puncture through the abdominal wall with a Silverman needle, after 1200 cc. of plasma had been given the day before. The total precipitable saline soluble liver protein was 8.73 Gm. per cent with an albumin fraction of 5.12 Gm. per cent and determined globulin fraction of 3.61 Gm. per cent. The saline insoluble protein was 7.89 Gm. per cent. At the time of operation another biopsy was obtained. The total precipitable saline soluble protein had risen to 10.01 Gm., with an albumin fraction of 4.64 Gm. and a globulin fraction of 4.57 Gm. per cent. The saline insoluble protein dropped to 4.26 Gm. per cent. That the protein concentration of the liver increased after the large plasma transfusions cannot be denied, but this does not necessarily indicate that intact plasma protein was stored as such.

The ratio of saline soluble to saline insoluble protein preoperatively was 1.10, operatively 2.37. This result seems to indicate that some of the infused protein was at least temporarily incorporated into the liver although it is difficult to state in what manner.

TOTAL SOLUBLE LIVER NITROGEN

Total soluble liver nitrogen was determined on all liver biopsy specimens. As a general rule, the total soluble liver nitrogen expressed as protein was in the neighborhood of 300 mg. per cent higher than the total protein N. A portion of this non-protein nitrogen is urea, creatinine, uric acid, etc. There is a possibility that the remaining components may be amino acids, polypeptides, proteoses, or other split protein products. These would be the "building blocks" for plasma protein synthesis. The significance of a single determination of total saline soluble liver nitrogen is difficult to interpret; with repeated successive biopsies it becomes of greater importance.

BLOOD URIC ACID LEVELS AS A CRITERION OF PROTEIN DEPLETION

A recent report[16] stated that blood uric acid levels were elevated in patients with hypoproteinemia secondary to gastric carcinoma and that the magnitude of the elevation was an index to the degree of protein deficiency. The rise in uric acid in their cases was interpreted as an attempt by the body to replenish the protein deficiency by means of an accelerated endogenous protein metabolism. Hyperuricemia was the evidence of this acceleration.

Plasma protein and blood uric acid levels were simultaneously obtained on 7 hypoproteinemic patients (Table III) and 20 normal patients (Table IV). In patients without hypoproteinemia and two patients with hypoproteinemia twenty-four hour uric acid excretion was studied. Determinations were made by the method of Folin.[22] There were no significant differences in uric acid blood levels or 24 hour excretion in the two groups.

TABLE IV.—*Clinical Diagnosis, Weight Loss, Blood Protein and Uric Acid Concentrations in Patients without Hypoproteinemia*

Patient's No.	Diagnosis	Wt. Loss in Pounds	Total Protein Gm. %	Blood Uric Acid Mg. %
2	Ca of pancreas	10 (6 wks.)	6.64	3.27
4	Ca of stomach	5 (6 mos.)	6.64	5.65
7	Lipoid dystrophy	0	6.40	6.68
8	Lipoid dystrophy	0	6.98	4.71
9	Ca of cardia	15 (4 mos.)	6.26	2.26
10	Ca of esophagus	12 (3 mos.)	7.78	4.17
11	Ca of pancreas	30 (6 mos.)	6.53	3.43
12	Closure of colostomy	30 (6 mos.)	6.58	4.17
13	Cardiospasm	0	6.70	4.84
14	Ca of stomach	0	6.77	3.74
15	Hemolytic anemia	15	6.16	3.90
*18	Ca of stomach	24 (2 mos.)	6.14	3.10
19	Ca of stomach	0	6.02	4.44
23	Normal	0	7.26	4.00
24	Normal	0	7.21	5.84
25	Normal	0	7.32	3.67
26	Normal	0	7.68	5.97
27	Normal	0	7.57	5.48
**28	Gastric ulcer	18 (10 days)	7.17	3.98
29	Cirrhosis	0	7.16	4.02

* 24 hour uric acid excretion 148.1 Mg. ** 24 hour uric acid excretion 325.9 Mg.

Lenox[23] demonstrated that uric acid is retained in fasting states and an increase to as much as 14 mg. per cent may occur after 5 days of fasting. Brochner-Mortensen[24] mentions disease processes in which uric acid blood levels may be elevated because of faulty excretion. It seems likely that if elevations in blood uric acid concentrations are occasionally found in hypoproteinemic patients they are purely on the basis of retention secondary to fasting.

The work of Schoenheimer[25] with isotopic nitrogen has disproved the concept that there is a separate endogenous and exogenous protein metabolism, but rather that there is a common "metabolic pool." It would seem likely that in hypoproteinemic patients, all metabolic processes involving protein are spared to the same extent, and the rate of protein metabolism becomes lowered.

DISCUSSION AND CONCLUSIONS

The protein reservoir in the form of total circulating plasma proteins although partially dependent upon the concentration of plasma proteins cannot be assessed by isolated plasma protein value. The total circulating protein per square meter of surface area is lower in hypoproteinemic patients.

The precipitable saline soluble liver protein per unit protein structural mass (ratio of precipitable saline soluble to saline insoluble protein) is maintained at a relatively constant level between 1 and 2 Gm. per Gm. of structural protein. The constancy of this ratio suggests that there are definite protein storage limitations in the liver and also that a certain quantity of precipitable saline soluble protein is retained by the liver cell for preservation of vital functions. The variations between 1 and 2 Gm. per unit structural mass allows for a maximum possible storage capacity of 2.28 Gm. of protein in a 1500 Gm. liver. That such storage actually occurs at least temporarily is illustrated by the one case receiving a large plasma and blood transfusion. Since most ratios of precipitable saline soluble to saline insoluble liver protein are maintained closely in the region of 1.5 it is unlikely that ratios raised by plasma infusions remain high for more than a short time. Because this ratio is fairly constant there is a relatively large stationary protein mass in the liver. Such a situation tends to mask any small changes in protein concentration which may occur, and may have led some investigators to feel that there is no relationship between blood and liver proteins.[26]

That liver proteins do participate in alterations occurring in plasma proteins in evident from the data presented. The rapidity with which changes may occur is demonstrable in the dog experiments.[19] The results of both studies are therefore in harmony.

SUMMARY

A study was conducted on patients in order to evaluate and correlate the effects of protein depletion upon total plasma protein, albumin and globulin, total circulating plasma protein and liver proteins. The significance of the various protein fractions of the liver has been discussed.

Blood uric acid determinations have little value as an index of protein depletion.

Thanks is expressed to Dr. D. B. Phemister for his assistance in the promotion of these studies. Thanks is also given to Mrs. Evelyn Gordon for her technical skill in the performance of the many determinations.

REFERENCES

1 Studley, H. O.: Percentage of Weight Loss a Basic Indicator of Surgical Risk in Patients with Peptic Ulcer. J. A. M. A. 106: 458, 1936.

2 Cannon, P. R., R. W. Wissler, R. L. Woolridge and E. P. Benditt: Relationship of Protein Deficiency to Infection. Ann. Surg. 120: 514, 1944.

3 Thompson, W. D., I. S. Ravdin and I. L. Frank: Effects of Hypoproteinemia on Wound Disruption. Arch. Surg., 36: 500, 1938.

4 Leigh, O. C. Jr.: Ileus Associated with Edema of the Bowel. Surg., Gynec. & Obst., 75: 279, 1942.

5 McHenry, E. W., and J. M. Patterson: Lipotropic Factors. Physiol. Rev., **24**: 128, 1944.
6 Mecray, P. M., R. P. Barden and I. S. Ravdin: Nutritional Edema: Its Effect on the Gastric Emptying Time Before and After Gastric Operations. Surgery **1**: 53, 1937.
7 Co Tui, A. M. Wright, J. H. Mulholland, V. Carabba, I. Barcham and V. J. Vinci: Studies on Surgical Convalescence 1. Sources of Nitrogen Loss Post Gastrectomy and Effect of High Amino-Acid and High Caloric Intake on Convalescence. Ann. Surg., **120**: 99, 1944.
8 Elman, R., and C. E. Lischer: Occurrence and Correction of Hypoproteinemia (Hypoalbuminemia) in Surgical Patients; Collective Review. Internat. Abstr. Surg., **76**: 503, 1943.
9 Cuthbertson, D. P.: Post-Shock Metabolic Response. Lancet, **1**: 433, 1942.
10 Taylor, F. H. L.: Protein Requirements Under Special Physiological Demands with Particular Relation to Burns, Penetrating Wounds, and Trauma. Buffalo Univ. Centennial Conference Lecture, Oct. 1946.
11 Sachar, L. A., A. Horvitz and R. Elman: Studies on Hypoalbuminemia Produced by Protein Deficient Diets. I. Hypoalbuminemia as a Quantitative Measure of Tissue Protein Depletion. J. Exper. Med., **75**: 453, 1942.
12 Peters, J. P.: Methods of Evaluation of Protein Deficiency. Buffalo Univ. Cent. Conference Lecture, Oct. 1946.
13 Addis, T., L. J. Poo and W. Lew: The Quantities of Protein Lost by the Various Organs and Tissues of the Body During a Fast. J. Biol. Chem., **115**: 111, 1936.
14 Elman, R., C. E. Lischer and H. W. Davy: Plasma Proteins (albumin and globulin) and Red Cell Volume following Single Severe Non-Fatal Hemorrhage. Am. J. Physiol., **138**: 569, 1943.
15 Madden, S. C., and G. H. Whipple: Plasma Proteins Their Source Production and Utilization. Physiol. Rev., **20**: 194, 1940.
16 Ficarra, B. J.: Hyperuricemia in Gastric Cancer. Surgery, **19**: 223, 1946.
17 Tripoli, C. J., and D. E. Fader: The Differential Diagnosis of Certain Diseases of the Liver by Means of a Punch Biopsy. Am. J. Clin. Path., **11**: 516, 1941.
18 Gregersen, M. I.: Practical Method for Determination of Blood Volume with Dye T-1824; Survey of Present Basis of Dye Method and Its Clinical Applications. J. Lab. and Clin. Med., **29**: 1266, 1944.
19 Fishman, W. H., and H. H. LeVeen: A Method of Partitioning Liver Proteins and Its Application to the Study of the Effects of Acute Hemorrhage in Dogs. In Press.
20 Gibson, J. G., 2nd and W. A. Evans, Jr.: Clinical Studies of Blood Volume; Relation of Plasma and Total Blood Volume to Venous Pressure, Blood Velocity Rate, Physical Measurements, Age and Sex in 90 Normal Humans. J. Clin. Investigation, **16**: 317, 1937.
21 Quiring, D. P.: Surface Area Determination. Med. Physics., 1490, 1944.
22 Folin, O.: Standardized Methods for Determination of Uric Acid in Unlaked Blood and in Urine. J. Biol. Chem., **101**: 111, 1933.
23 Lennox, W. G.: A Study of the Retention of Uric Acid During Fasting. J. Biol. Chem., **66**: 521, 1925.
24 Brochner-Mortensen, K.: The Uric Acid Content in Blood and Urine in Health and Disease. Medicine, **19**: 161, 1940.
25 Schoenheimer, R.: The Dynamic State of Body Constituents. Cambridge, Mass. Harvard University Press, 1942.
26 Ariel, I. M., J. C. Abels, H. Murphy, G. T. Pack, C. P. Rhoads: Metabolic Studies in Patients with Cancer of the Gastro-Intestinal Tract. VIII. The Chemical Composition of the Liver, Especially in Patients with Gastrointestinal Cancer. Ann. Int. Med., **20**: 570, 1944.

N. Y. Univ., College of Medicine
477 First Avenue, New York 16, N. Y.

A SIMPLIFICATION OF THE DIAGNOSIS OF VARICOSE VEINS*

CHARLES A. STEINER, M.D., AND LOUIS H. PALMER, M.D.
UPPER DARBY, PA.

AS OUR KNOWLEDGE of the pathologic physiology of varicose veins has increased throughout the years, numerous tests have been introduced into the literature which were designed to facilitate the diagnosis and treatment of this condition. It is evident from teaching experience, as well as from contact with the practicing physician, that the performance and interpretation of these tests appears to be a formidable undertaking which is discouraging to the new student, and far too time-consuming for the average busy practitioner to master.

In every treatise on the subject of varicose veins, one encounters a description of the following tests, the understanding of which would appear to be absolutely necessary before intelligent treatment could be undertaken:

1. Brodie-Trendelenburg Test.
2. Comparative Tourniquet Test (Ochsner and Mahorner).
3. Perthes' Test.
4. Compression Test.
5. Schwartz Test (Percussion Test).

It would now appear that two of these tests have become obsolete and could well be disposed of entirely, and that one or two others are of largely academic interest. With this in mind, it was felt that a paper which might simplify the diagnosis and certain aspects of the treatment of varicose veins would be timely.

AN EVALUATION OF THE COMMONLY ACCEPTED DIAGNOSTIC TESTS

The above tests will be considered individually as to their performance, interpretation, and relative merit. Since most of our readers will be somewhat familiar with these tests, the description of the technic and interpretation will be somewhat brief.

1. BRODIE-TRENDELENBURG TEST

This test was originally described by Brodie[1] in 1846, and popularized by Trendelenburg[2] in 1891. As originally described by Brodie and Trendelenburg, the test was devised only to demonstrate an incompetency at the saphenofemoral junction. Since that time, however, numerous modifications have been introduced so that the present interpretation is much more comprehensive. The following is a brief summary of the performance and interpretation of the test:

Technic: The affected leg is elevated and the veins emptied by gravity. A tourniquet is then applied around the upper thigh, sufficiently tight to constrict the saphenous vein,

* This paper is based upon the personal treatment of over 3,000 patients with varicose veins and their complications at the Woman's Medical College, Bryn Mawr, and Delaware County Hospitals during the past ten years.

but not the femoral vein. The patient then stands upright, and the degree of filling of the saphenous vein is noted with the tourniquet in place and again with the tourniquet removed.

Interpretation.—Negative: A negative test is one in which, with the tourniquet in place, the veins fill within a period of 30 seconds, and upon removal of the tourniquet, no increased rate of filling is observed (Fig. 1). Here, it is apparent that no retrograde flow is taking place through the saphenofemoral junction, and that the filling was due to an incompetency of the communicating veins.

Positive: In a positive Brodie-Trendelenburg test, when the patient stands with the tourniquet in place, the varicosities will remain collapsed throughout the 30-second

FIG. 1.—STEP I: *Negative Brodie-Trendelenburg Test*

(A) Tourniquet On: Varicosities distended at end of 30-second period due to reflux from communicating veins.

(B) Tourniquet Off: No further distention of varicosities upon removal of tourniquet, indicating competency at the saphenofemoral junction.

FIG. 2.—STEP I: *Positive Brodie-Trendelenburg Test*

(A) Tourniquet On: The varicosities remain collapsed throughout the 30-second period.

(B) Tourniquet Off: Rapid filling of the veins occurs from above indicating incompetency of the valves at the saphenofemoral junction.

period, but upon release of the tourniquet, the internal saphenous rapidly fills with blood from above (Fig. 2). Here, the valves in the saphenous vein at the saphenofemoral junction are incompetent, although the valves of the communicating veins are still intact.

Doubly-Positive: A so-called doubly-positive test is one in which, with the tourniquet in place, the veins fill rapidly, and with the release of the tourniquet, even further distention of the veins takes place. In this case, the valves at the saphenofemoral junction as well as the valves of one or more communicating veins are incompetent.

Nil: In a Trendelenburg-nil test, with the tourniquet in place, and again with the tourniquet removed, there is only slow filling of the veins from below. This would indicate competency of the valves of both the saphenous and communicating systems of veins.

It might be mentioned that considerable confusion exists in the literature between the Trendelenburg-negative and the Trendelenburg-nil tests as described above. In view of the fact that the Trendelenburg-nil demonstrates competency of the valves of both the

saphenous and communicating systems of veins, it would seem that such an individual would not have true varicose veins, and that this part of the interpretation of the test is unimportant.

This test accomplishes two purposes: First, it demonstrates any existing retrograde flow of blood through the saphenofemoral junction. Secondly, it indicates the presence of one or more incompetent communicating veins between the superficial and deep venous systems, although it does not establish the level of such a vein. By its use, therefore, one may determine whether or not high ligation of the saphenous and its branches is indicated, and, secondly, whether or not an additional ligation at a lower level is necessary.

II. COMPARATIVE TOURNIQUET TEST (OCHSNER AND MAHORNER)

This test was described by Ochsner and Mahorner[3] in 1936 as follows:

Technic: The patient is draped so that both thighs and legs are visible, and he then stands before the observer who notes the size of the varicosities. The patient then walks to and fro, and the examiner again observes the prominence of the veins. Following this, a tourniquet is applied to the upper third of the thigh sufficiently tight to constrict the superficial, but not the deep veins, and again the size of the varicosities is noted with the patient walking. The same procedure is followed with the tourniquet applied to the middle, and finally to the lower third of the thigh.

Interpretation.—The interpretation of this test with the tourniquet at the upper third of the thigh is exactly similar to the Brodie-Trendelenburg test in that it demonstrates the relative competency of the valves of the saphenofemoral junction, and also designates whether or not any incompetent communicating veins exist lower in the thigh. The application of tourniquets lower in the thigh serves to designate the level of entrance of any existing communicating veins into the superficial system. Also, these tourniquets by occluding the superficial veins, would serve to reveal the presence of a deep femoral thrombosis, the theory being that if the deep veins were occluded by thrombus and the superficial veins by tourniquets, blood could no longer escape from the lower leg, and the varicosities present would tend to increase rather than decrease in size as the patient walks.

This test properly performed actually affords quite complete information as to the status of the superficial and deep venous circulations of the leg. However, much of the information obtained from this test is of purely academic interest, and is actually not essential to the intelligent management of the varicose vein patient. For example, one can demonstrate an incompetency at the saphenofemoral junction even more clearly in the Brodie-Trendelenburg test than in this test. One has also learned from the Brodie-Trendelenburg test whether or not any incompetent communicating veins exist below the level of the tourniquet. The actual level at which such an incompetent communicating vein exists is, in most instances, unimportant, since once the presence of such a vein has been established, low ligation of the internal saphenous below all of the communicating veins in the thigh will produce the desired result in the lower leg. The segment of dilated vein in the thigh extending from the incompetent communicating vein to the level of the low ligation can nearly always be satisfactorily obliterated by subsequent injection therapy. In the occasional case where such a varicosity would seem to persist, ligation of that communi-

cating vein might be advisable, but it has been our experience that the Mahorner-Ochsner test does not accurately localize its exact site. We have instead determined this level by marking the uppermost portion of the dilated segment, and making a vertical incision in this area through which the dilated vein is dissected upward to the site of the communicating vein which is then ligated.

A practical simplification of the Mahorner-Ochsner test, therefore, would be to perform the Brodie-Trendelenburg test, which, as stated previously,

FIG. 3.—STEP I: *Doubly-Positive Brodie-Trendelenburg Test*

(A) Tourniquet On: Some filling of the veins occurs within 30 seconds due to a reflux through incompetent communicating veins.

(B) Tourniquet Off: Further filling of the varicosities occurs due to incompetency at the saphenofemoral junction.

FIG. 4.—STEP II: *Tourniquet Above Knee*

(A) Varicosities collapsed because incompetent communicating veins lie above tourniquet.

(B) Varicosities distended because incompetent veins exist below the level of the tourniquet.

demonstrates the presence of any existing communicating veins, following which a single tourniquet is applied just above the knee which will indicate whether the incompetent communicating veins lie above or below this level (Fig. 4). If above this level, ligation just above the knee is indicated in addition to ligation of the saphenous at the saphenofemoral junction. In other words, by performing the Brodie-Trendelenburg test with this modification, the comparative tourniquet test is unnecessary insofar as its value in determining the type of treatment indicated is concerned. The value of the part of the comparative tourniquet test which deals with the status of the deep circulation of the leg will be discussed later.

III. PERTHES' TEST

Perthes[4] described this test, in 1895, as a clinical method of evaluating the status of the deep circulation in the leg.

Technic: With the patient standing, a tourniquet is applied just above the knee sufficiently tight to constrict the superficial veins of the leg, and the size of the varicosities in the lower leg is noted. The patient walks fairly rapidly to and fro before the observer, who continues to note the prominence of the varicosities.

Interpretation.—Perthes interpreted this test in the following manner: If the deep venous system is patent, the superficial veins will actually become smaller due to the blood in them being drawn into the deep system. If the deep system is not patent, the superficial veins become more prominent since the blood has no way of escaping from the lower leg as both the superficial and deep systems are blocked.

Actually, a distinct fallacy in this test is the fact that occlusion of the deep circulation would have to exist at the exact level of the tourniquet for a positive test to be obtained. If an occlusion existed above or below the level of the tourniquet, a negative test might well result. Furthermore, as will be shown later, a knowledge of the status of the deep venous circulation is not essential to adequately treat the varicose vein patient. It is, therefore, evident that this test has little to recommend it, and may be discarded from future use.

IV. COMPRESSION TEST

This test has been recommended as an additional method of determining the patency of the deep venous system of the lower leg.

Technic: A compression bandage is applied from the toes to the knee just sufficiently tight to obliterate the superficial veins. Patient then walks for 30 minutes without stopping.

Interpretation.—As was pointed out above, the Perthes' test revealed an obstruction only at the level of the application of the tourniquet, while this test was intended to reveal an obstruction at any level of the deep venous system of the lower leg. It was supposed that the compression bandage by obliterating the superficial veins, here, again, demanded that all of the blood in the lower leg must return through the deep venous system. If the deep venous system was obstructed by thrombus, the patient would complain of a cramp-like pain before the 30-minute period had elapsed since it was believed that the blood could not leave the leg through either the superficial or the deep veins. If the deep veins were open, the patient would be able to walk comfortably throughout the 30-minute period.

This test is impractical for two reasons: First, the time required for the performance of the test would prevent its general use; and, secondly, it is extremely difficult to apply the compression bandage with just the proper degree of compression. Moreover, as stated above, it will be shown that a knowledge of the status of the deep venous circulation is not essential in the treatment of varicose veins. Therefore, this test would seem to have little to recommend it, and we feel that it should likewise be discarded.

V. SCHWARTZ TEST (PERCUSSION TEST)

This test was described by Schwartz[5] in 1897 as follows:

Technic: The fingers of one hand are placed over the saphenous vein at the saphenofemoral junction. A varicosity above or below the knee is percussed with the fingers of the opposite hand.

Interpretation.—If the valves of the saphenous vein are incompetent, an impulse is transmitted to the uppermost hand.

The results of this test are frequently unreliable, and any information obtained from it is more readily available from the Brodie-Trendelenburg test. Furthermore, Mahorner and Ochsner state that Ledderhose[6] has quite conclusively shown that such a transmitted impulse is a normal finding in a competent saphenous vein. For these reasons, this test can certainly be eliminated from future use.

COMMENT: A review of the above would indicate that the Perthes', compression, and Schwartz tests have little to offer, are unreliable, and reveal no information which cannot be obtained by more accurate methods, and it is, therefore, our feeling that they no longer have a place in the diagnosis and treatment of varicose veins. It would seem that the Brodie-Trendelenburg test, with the additional feature of the tourniquet placed just above the level of the knee, as described above, will actually afford all of the information required for one to treat any uncomplicated case of varicose veins. As will be shown later, it is not even necessary to determine the patency of the deep venous circulation in order to institute adequate therapy.

DISCUSSION WITH RESPECT TO THE NECESSITY FOR THE EVAULATION OF THE DEEP VENOUS CIRCULATION

Throughout the literature, the determination of the status of the deep venous circulation has always been considered necessary before any effort was made to obliterate existing superficial veins. It was assumed that these superficial veins might be acting as collateral circulation around a point of obstruction in the deep venous system, in which case obliteration therapy would be contraindicated.

It has always seemed unlikely to us, however, that dilated, tortuous superficial veins, that is, typical varicose veins, whose valves must obviously be incompetent, could actually carry blood against the effect of gravity around a deep femoral thrombosis. Furthermore, it is difficult to understand how veins can be acting as collateral circulation when the Brodie-Trendelenburg test indicates a reversed flow of blood through them. It would rather seem, therefore, that if the deep system of veins is occluded, and if the Brodie-Trendelenburg indicates a retrograde flow of blood through the visible varicosities, there must be an intermediate system of collateral veins present to enable blood to escape from the leg. Thus, it would seem that in any case in which a retrograde flow of blood can be demonstrated by the augmented Brodie-Trendelenburg test described above, irrespective of the status of the deep circulation, not only will no harm be done by ligation, but, actually, the usual benefit to the varicose

veins from this treatment should be expected, and even further improvement in the extremity obtained by lessening the load carried by the true collateral circulation. We might add that by eliminating the varicose veins present, one will diminish the tendency for superficial phlebitis (phlebitis migrans) to develop as it so frequently does in patients who have had a deep femoral thrombosis.

It might be mentioned in further support of this theory, that simultaneous ligations of both the superficial and deep venous systems are routinely done by

FIG. 5.—STEP III: *Tourniquet Below Knee*

(A) Varicosities collapsed because incompetency exists at entrance of short saphenous into the popliteal above level of tourniquet.

(B) Varicosities distended because incompetent communicating veins exist below level of tourniquet.

many of us in the active treatment of phlebothrombosis with no untoward results. Furthermore, in phlebothrombosis, one is dealing with veins which were essentially normal until the thrombosis occurred; that is, no time-interval for the development of a collateral circulation existed as it does in the case of chronic deep vein thrombosis.

SUGGESTED APPROACH TO DIAGNOSIS

When the new patient appears for examination, the usual history and physical examination are done. A diagnosis of varicose veins having been established, the following procedure is suggested:

Step I: The Brodie-Trendelenburg test is performed, after which one should know the status of the valves of the saphenofemoral junction as well as the existence of any communicating veins below this level.

If the Brodie-Trendelenburg test is negative (Fig. 1), indicating that the valves of the saphenofemoral junction are intact, but that one or more incompetent communicating veins exist below the level of the tourniquet, the next step is performed.

Step II: The Brodie-Trendelenburg test is repeated with the tourniquet applied just above the knee instead of at the saphenofemoral junction (Fig. 4). If the varicosities remain collapsed, one may assume that all incompetent communicating veins lie above the level of the tourniquet, and ligation of the saphenous just above the knee is indicated. It has been our experience that ligation here, without a ligation of the saphenous at the saphenofemoral junction, does not produce a complete nor permanent result, and in such cases it has been our custom to perform a high ligation of the saphenous, with its branches in addition. As was stated in the discussion of the Mahorner-Ochsner test, "the segment of dilated vein in the thigh extending from the incompetent communicating vein to the level of the low ligation can nearly always be satisfactorily obliterated by subsequent injection therapy. In the occasional case where such a varicosity would seem to persist ligation of that communicating vein might be advisable." This is accomplished by marking the uppermost portion of the dilated segment and making a vertical incision through which the dilated vein is dissected upward to the site of the communicating vein which is then ligated and the dilated segment itself is excised.

If, on the other hand, the varicosities fill as rapidly as before the application of the lower tourniquet, one of two possible causes exists: (1) A retrograde flow of blood may take place from the popliteal vein to the external saphenous; or (2) a retrograde flow of blood may pass from the deep to the superficial veins of the calf through the communicating veins of the lower leg. In either event, one further step is then indicated.

Step III: The Brodie-Trendelenburg test is again repeated, this time with the tourniquet just below the level of the entrance of the external saphenous vein into the popliteal vein (Fig. 5). If the veins now remain collapsed with the tourniquet in place, one may assume that a valvular incompetency exists at the entrance of the short (external) saphenous into the popliteal, and ligation should be performed at this point. Should the veins, however, fill as rapidly as before, one assumes that the incompetency exists in the communicating veins of the lower leg and injection therapy alone will produce a satisfactory result in nearly every instance. Here again, if a dilated vein should persist after several injections, local excision of this vein and ligation of the communicating vein through a vertical incision can easily be done.

If the Brodie-Trendelenburg test is positive at the saphenofemoral junction (Fig. 2), indicating incompetency of the valves at this site, one immediately knows that high ligation alone is indicated. Occasionally a few supplementary injections may be necessary if any residual varicosities exist when this has been done.

If the Brodie-Trendelenburg test is doubly-positive (Fig. 3), indicating an incompetency of the valves both at the saphenofemoral junction and in the communicating veins below this level, one knows at once that high ligation is indicated, but Step II, and possibly Step III, will be required to disclose the type of supplementary therapy necessary. The performance and interpretation of these steps has been described under "negative Brodie-Trendelenburg test."

Since we have shown above that there is no need to determine the status of the deep circulation, the clinical examination of the varicose vein patient is completed at this point. However, there are occasional cases where actual roentgenographic visualization of the veins of the leg is necessary to arrive at the proper plan of therapy. We have found venographic studies to be helpful in the following instances: 1. Where swelling, induration and obesity have rendered certain features of the clinical examination inconclusive. 2. Where patients have responded poorly to adequate therapy, venograms have occa-

sionally demonstrated an undetected incompetent communicating vein, or an anomalous saphenous vein.

SUMMARY

I. From teaching experience, as well as from contact with the practicing physician, it is evident that much confusion exists with respect to the diagnostic procedures which have been described in the treatment of varicose veins. Since the institution of appropriate therapy depends entirely upon an accurate diagnosis, this phase of the subject is particularly important.

II. A reëvaluation of the five tests commonly described in every treatise on this subject reveals that three of them, namely the Perthes', compression, and Schwartz tests, have become obsolete and should be discarded from future use. A fourth test, the Mahorner-Ochsner (comparative tourniquet test), while affording quite complete information about the status of the superficial and deep circulations of the leg, is somewhat complicated, and the information revealed is of largely academic interest.

III. The importance of determining the patency of the deep venous circulation in the treatment of varicose veins has been overemphasized, and the complicated tests described to elicit this information have added much to the confusion of the examiner. It is our belief, that irrespective of the status of the deep circulation, if true varicose veins are present, they should be treated as such.

IV. A simplified approach to diagnosis, which requires little special knowledge, and which may readily be performed as a simple office procedure, is described.

REFERENCES

1 Brodie, Sir B.: Lectures Illustrative of Various Subjects in Pathology and Surgery, 7, 411, 1846, London, Longmans Green & Co.

2 Trendelenburg, J.: Über die Unterbindung der Vena saphena magna bei Unterschenkelvaricen. Beitr. z. klin. Chir., 7, 195, 1890–1891.

3 Mahorner, H. R., and Ochsner, Alton: A New Test for Evaluating Circulation in the Venous System of the Lower Extremity Affected by Varicosities. Arch. Surg., 33, 479, 1936.

4 Perthes, Georg: Über die Operation der Unterschenkelvaricen nach Trendelenburg. Deutsche med. Wehnschr., 21, 253, 1895.

5 Schwartz: Traite de Cherur., LeDentu-Delbet, IV, 1897.

6 Ledderhose: Varicose Veins, Mahorner, H. R., and Ochsner, Alton, 1939, C. V. Mosby Company.

7 McPheeters, H. O., and Anderson, J. K.: Injection Treatment of Varicose Veins and Hemorrhoids. 1938, F. A. Davis Co.

8 Shelley, H. J.: Sclerosing Therapy, 1939, Williams & Wilkins Co.

9 Linton, R. R.: The Communicating Veins of the Lower Leg and the Operative Technic for their Ligation. ANNALS OF SURGERY, 107, No. 4, 582, April, 1938.

10 McPheeters, H. O.: Varicose Veins: The Injection Versus the Operative Treatment. S. G. O., 48, 819–822, June, 1929.

11 McCallig, J. J., and Heyerdale, W. W.: A Basic Understanding of Varicose Veins. J. A. M. A., 115, 97, July 13, 1940.

12 Baker, E. C., and Sedwitz, S. H.: Observations on Venography of the Lower Extremities. Radiology, **41**, No. 5, 451–458, November, 1943.

13 Heyerdale, W. W., and Stalker, L. K.: Management of Varicose Veins of the Lower Extremities. ANNALS OF SURGERY, **114**, 1042, December, 1941.

14 Farquharson, E. L.: Treatment of Varicose Veins in Soldiers. British Med. Jour., **2**, 453, October 17, 1942.

15 McPheeters, H. O.: The "Do's and Don'ts" of the Injection Treatment of Varicose Veins. Minn. Med., **17**, 33, January, 1934.

16 Sarma, P. J.: Recurrences and Failures following the Modern Treatment of Varicose Veins. Surgery, **10**, 752, November, 1941.

17 Stalker, L. K., and Heyerdale, W. W.: Factors in Recurrence of Varicosities following Treatment. S. G. O., **71**, 723, December, 1940.

18 Vaughn, A. M.: Varicose Veins. Ill. Med. Jour., **78**, 137, August, 1940.

19 Sears, J. B., and Cohen, S. S.: The Treatment of Varicose Veins by High Division and Retrograde Injection. S. G. O., **70**, 842, April, 1940.

20 Wright, A. D.: Treatment of Varicose Veins. British Med. Jour., **1**, 665, April 20, 1940.

21 Barrow, Woolfolk: The Treatment of Varicose Veins in the Lower Extremity. Ky. Med. Jour., **38**, 140, April, 1940.

22 Dean, G. O.: Treatment of Varicose Veins at the University Hospitals. J. Iowa State Med. Soc., **30**, 8, January, 1940.

23 Rogers, Lambert: Varicosities of Veins: Choice of Treatment, and End-results. British Med. J., **2**, 383, August 19, 1939.

24 Mahorner, H. R., and Ochsner, Alton: The Modern Treatment of Varicose Veins as Indicated by the Comparative Tourniquet Test. ANNALS OF SURGERY, **107**, 927, June, 1938.

25 Lawes, C. H. W.: Some Recent Views on Varicose Veins of the Lower Limb. Med. J. of Australia, **1**, 509, April 13, 1940.

26 Scurry, C. J.: Surgical Treatment of Varicose Veins. J. So. Car. Med. Ass'n, **38**, 60, March, 1942.

27 Vaughn, A. M.: Varicose Veins. Ill. Med. J., **78**, 137, August, 1940.

28 McPheeters, H. O.: The Present Status of the Management of Varicose Veins. Int. Abs. Surg., **67**, 494–498, November, 1938.

29 Pearce, M. B.: Varicose Veins. Surgery, **14**, No. 6, 901–914, December, 1943.

30 Howard, N. J., Jackson, C. R., and Mahon, E. J.: Recurrence of Varicose Veins Following Injection. Arch. Surg., **22**, 353–376, March, 1931.

31 Starr, A., Frank, H. A., and Fine, J.: The Venographic Diagnosis of Thrombophlebitis of the Lower Extremities. J. A. M. A., **118**, 1192, April 4, 1942.

32 Lesser, A., and Danelius, G.: Venography: Its Value in the Diagnosis and Management of Venous Disturbances of the Lower Extremities. ANNALS OF SURGERY, **119**, No. 6, 903, June, 1944.

Upper Darby National Bank Bldg.
Upper Darby, Pa.

GIANT INTRACANALICULAR FIBRO-ADENOMA OF THE BREAST

Report of a Case

JAMES C. CLARKE, M.D.

LA GRANGE, ILL.

FROM THE DEPARTMENT OF SURGERY, THE MCNEAL MEMORIAL HOSPITAL, BERWYN, ILLINOIS

ADVANCED CASES OF INTRACANALICULAR FIBRO-ADENOMA of the breast present a bulky, freely movable, encapsulated, nodulated, often ulcerated and fungating tumor. In 1827, Cumin[1] reported the first case recorded in medical literature of a large breast tumor of "firm cystic with intracystic fungoid growths." In 1931 Lee and Pack,[4] in an exhaustive review of the literature since Cumin's case, collected 105 similar cases and reported four of their own. MacKenzie,[5] in 1935, reported a 24.6 pound "adenofibroma of the breast." Owens and Adams,[6] 1941, collected 12 more cases from the literature of the preceding decade and added one of their own, bringing the total reported at that time up to 123. As nearly as can be determined from the descriptions of all the reported cases, only 10 of these tumors exceeded in size and weight that of the case reported in this paper.

Many names have been given to this type of tumor, each emphasizing one aspect of its protean nature. All of these were listed in the report of Owens and Adams[6] and will not be repeated. The consensus of opinion now is that the most accurate terminology is intracanalicular fibro-adenoma, characterized in the late stages by myxomatous degeneration. Because of this myxomatous degeneration, these late cases have been called "intracanalicular myxoma and cystosarcoma phyllodes." However, since these tumors are not truly malignant, this nomenclature is misleading. Although sarcomatous degeneration may occur, it usually does not, even when the tumor has existed for many years.

REPORT OF A CASE

Mrs. A. C., the patient, was 52 years old, white, married and nulliparous. Her mother had had a goitre. The family and past history were otherwise irrelevant. Upon admission to the hospital, July 19, 1944, her chief complaint was an enormous tumor of the right breast (Figs. 1 and 2). Thirteen years ago, she discovered a lump in her right breast, which gradually increased in size, until she could no longer endure it, because of its size and weight. Three and one-half years ago the tumor began to ulcerate and exude a bloody serum from the raw surface requiring daily dressings. During the past five years she had lost 25 pounds weight and had noticed increasing nervousness. Palpitation and insomnia had been present for two years. In the past four months marked weakness had developed. There had been no diarrhea.

Physical examination revealed an anemic, poorly nourished, white female, not acutely ill. She was 5 feet 5½ inches tall and weighed 119 pounds. Her temperature was 100.2 degrees, pulse 100, and respiratory rate 20. There was no lagophthalmos or exophthalmos and the pupils were equal and reacted to light and accommodation. There was a marked diffuse hyperplasia of both lobes and isthmus of the thyroid and a fine tremor of both hands.

FIG. 2.—Lateral view—Note pedunculation of tumor and dilated veins of pedicle, also goitre.

FIG. 1.—Anterior view—Note complete ulceration and bosselation of whole breast; also enormously dilated veins of chest wall.

There was an enormous tumor of the right breast, 6 x 9 x 10 inches in diameters. Most of its surface was raw, fungating and nodulated with only a rim of skin around the periphery. It was of solid consistency, very heavy and hung freely on a pedicle of skin. There were no palpable axillary lymph glands. The heart was slightly enlarged, the left border being just outside the midaxillary line. The rhythm was regular. There was a loud systolic aortic murmur. The rate was 100 to 110. Blood pressure was 138/70. The reflexes were hyperactive. There was no edema of the extremities. Physical examination was otherwise negative.

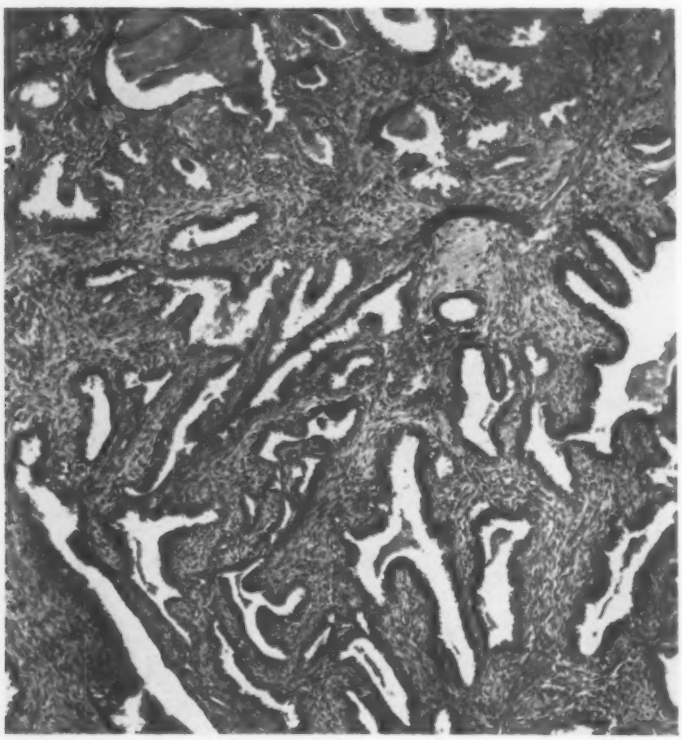


FIG. 3.—Low power. Adeno-fibroma of breast. Glandular, papillary, fibrous structure, secretory in type.

The urine was negative. Hemoglobin was 43.9 per cent or 6.80 Gms. Red cells 3,300,000, leucocytes 8,000, P-72 per cent, L-24 per cent, M-4 per cent. B.M.R. was plus 43 per cent. A roentgen-ray examination revealed a 4 per cent enlargement of the heart and generally increased lung markings. E.K.G.-rhythm was normal. There was evidence of a partial A.V. block, and a left axis deviation. The diagnosis of adenofibroma of the right breast, toxic adenoma of the thyroid and arteriosclerotic heart disease, was made.

Four days after admission to the hospital a simple right mastectomy was performed under nitrous oxide and oxygen anesthesia. On the second postoperative day the temperature dropped to normal and remained there. She was then put on ten drops of Lugol's solution t.i.d., p.c. and three capsules of liver and iron q.i.d. and sent home. Three weeks after the mastectomy she returned to the hospital weighing 100 pounds, and a subtotal thyroidectomy was performed.

The pathologic study was made by A. H. Baugher, M. D. The specimen consists of a mass weighing ten pounds and measuring 22 x 21 x 14 centimeters. It is incompletely

surrounded and covered by skin which shows many ulcerating areas. These areas vary in diameters up to seven centimeters, and have the general appearance of a granulating surface. On gross sectioning this tumor mass is found to be composed of numerous nodular, somewhat discreet, masses of tissue. These nodular masses are yellowish-gray, soft, and fibrous. Many hemorrhagic areas are found throughout. These vary in size up to several centimeters in diameter. Necrotic and cystic changes are also found throughout. Grossly, the above structures represent a right breast which has become excessively large, pendulous, and ulcerated. The pedicle measures five centimeters in each diameter and three centimeters in length.

FIG. 4.—High power. Adeno-fibroma of breast. (High power of #3). Note colloid of myxomatous degeneration.

Histologic sections show a predominant and marked overgrowth of the glandular elements. The stroma also shows marked hyperplasia. The glands are lined by a uniform epithelium which is secretory in type. These epithelial elements frequently show a papillary growth into definite alveoli and distended tubules. The basement membrane is intact. Many of the distended alveoli contain an eosin staining material. The interstitial fibrous connective tissue shows moderate periacinous proliferation and moderate myxomatous degenerative changes. The diagnosis is benign, pendulous, intra- and peri-canalicular adenofibroma of right breast (Figs. 3 and 4). Study of the thyroid gland reveals an adenomatous colloid hyperplasia of the thyroid.

Six weeks later the patient's basal metabolic rate was plus 12 per cent and her weight 124 pounds. Seven months after thyroidectomy her weight was 150 pounds, her normal weight. Up to the present time the patient is in good health.

CONCLUSION

1. An unusual case of giant fibro-adenoma of the breast weighing ten pounds is reported.

2. There was a concomitant toxic adenoma of the thyroid which masked the picture.

REFERENCES

1 Cumin, W.: Diseases of the mamma. Edinburgh Med. Jour., **27**: 229–231, 1827.

2 de Cholnoky, Tibor: Benign Tumors of the Breast. Arch. Surg., **38**: 79–98, 1939.

3 Hopkins, F. S.: A Large Fibro-adenoma of the Breast. N. E. Jour. Med., **223**: 53–54, 1940.

4 Lee, B. J., and G. T. Pack: Giant Intracanalicular Fibro-adenomyxoma of the Breast. The so-called cystosarcoma phyllodes mammae of Johannes Muller. Am. Jour. of Cancer, **15**: 2583–2609, 1931.

5 MacKenzie, K.: Brit. Jour. Surg., **23**: 235, 1935.

6 Owens, T. M., and W. E. Adams: Giant Intracanalicular Fibro-adenoma of the Breast. Archives of Surgery, **43**: 588–598, 1941.

La Grange Theatre Bldg.
La Grange, Illinois

MASSIVE RESECTION OF THE SMALL INTESTINE

H. D. COGSWELL, M.D.
TUCSON, ARIZONA*

WHEN A SITUATION presents itself, requiring excision of a large segment of small bowel, the "surgeon is confronted with the alternative of allowing the patient to die or resorting to a heroic effort to save the individual by resection."[1] Such cases are never of an elective nature and are encountered so rarely that I quote Holman[2] to introduce the following report. "The following case history may lighten the anxieties of other surgeons who may have to undertake resection on a heroic scale. At the time of operation imperfect acquaintance with the published work led me to take a gloomy view of the patient's prospects."

CASE REPORT

Mrs. H. C., a female, age 48, entered the hospital on July 7, 1946, in shock complaining of severe pain in the epigastrium which radiated to the back.

The patient had been under treatment for rheumatic heart disease for the past several years and had been confined to bed for most of the time during the past year. For this reason she had recently come to Arizona. Four days before admission the patient had noted epigastric distress with abdominal cramping and diarrhea. On the morning of entrance to the hospital the patient had a sudden attack of severe pain in the epigastrium followed by nausea, vomiting and collapse. When seen by her physician, Dr. Norman Jacobson, she had a blood pressure of 60/40, respiration 32, a pulse rate of 140 and was pale and perspiring. Both lungs were moist, with rales in the bases. Sinus arrythmia, enlargement of the heart to the left, and a loud systolic and diastolic murmur at the apex was present. The abdomen was distended with marked tenderness over the epigastrium. Bowel sounds were absent. No fluid level could be ballotted or percussed. No involuntary rigidity was present. Rectal and pelvic examinations revealed no abnormalities.

Serum amylase was 17 mgs. (normal 20–40 mgs.) R.B.C. 4,870,000; Hb. 15 Gm.; W.B.C. 10,960; Stab. 14; Seg. 59; Lymph 27; Urine (Voided) albumin 2 plus; leucocytes 2–4; erythrocytes, neg.

Roentgenograms of chest "Suggest old rheumatic heart with left auricular enlargement." Roentgenogram of abdomen—"Liver moderately enlarged, distention of major portion of small bowel. No free air in abdomen."

Clinical Diagnosis. Mesenteric thrombosis.

Operation. Under general anesthesia left paramedian incision was made, and on opening the peritoneal cavity a moderate amount of "port wine colored" fluid was found, having a putrid odor. Most of the small intestine was found to be gangrenous. There was no evidence of spillage from the bowel, but there was a good deal of the bloody serous material present in the cul-de-sac. For 14 inches from the ligament of Treitz the jejunum appeared viable. The bowel was then traced distally toward the cecum, and it was found that there was no further viable bowel remaining to the cecum; the cecum itself was discolored and there was some question about whether its circulation was ample. Resection of the entire small intestine with exception of about 14 inches of the jejunum and

* Thomas-Davis Clinic.

the duodenum was done. The intestine was resected up to the cecum and this area was inverted with three layers of sutures. The portion of the jejunum remaining was then brought to the ascending colon and an end-to-side anastomosis made, using three layers of sutures. The mesentery was tied with #1 plain catgut. The patient withstood this rather well, her condition being maintained by intravenous blood during the operation. The abdomen was closed in layers. One penrose drain was left in the subcutaneous tissue.

Post Operative Diagnosis. Arterial embolism of the superior mesenteric artery with gangrene of the greater portion of the small intestine.

Pathologic Report. Gross: Specimen consists of a portion of small intestine 310 cm. in length. Much of the intestine and attached mesentery are very dark in color, giving the appearance of beginning gangrene. The small blood vessels are filled with blood clot.

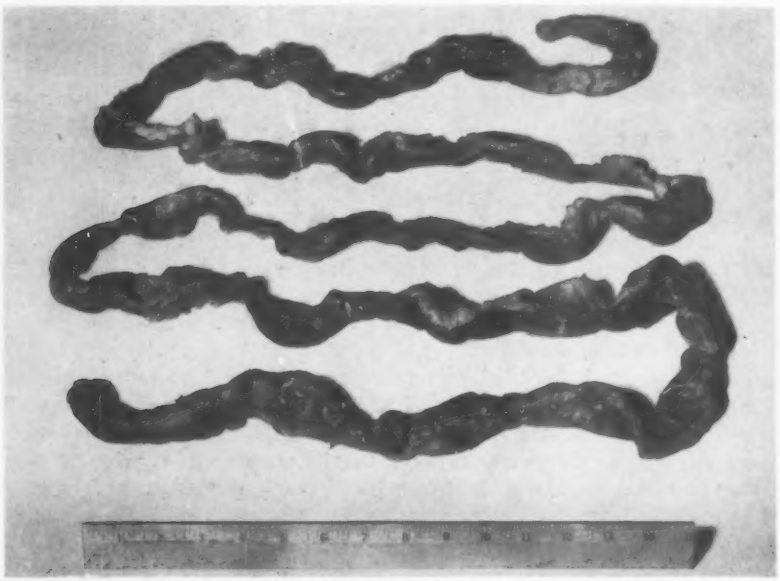


FIG. 1.—Photograph showing the intestine removed at operation.

Microscopic: There is marked extravasation of blood into the tissue of the mesentery. Small blood vessels are filled with organized blood clot.

Diagnosis: Mesenteric thrombosis.

Wangensteen nasal suction, constant O_2, intravenous fluids, transfusions, digifolin and penicillin 20,000 units every three hours were begun. Heparin was instituted on the first postoperative day with exercises on pedals. Nasal suction was discontinued on 7–12–46, on which day she passed several liquid stools. The temperature varied from 99 to 102 degrees the first week, then declined to normal. On 7–14–46 the patient had moderate bleeding from her incision and heparin was discontinued. On 7–15–46, the blood cholesterol was 118 mg./100 cc. (Normal 150–200 mg./100 cc.) The patient was given a high protein, low fat diet and had from four to eight liquid, foul stools daily. On 7–26–46 it was observed that the patient had mild carpopedal spasm. On the same day the blood calcium was 7.7 mg. per 100 cc., a plasma protein was 7 Gm. per 100 cc., and a glucose tolerance test was normal. Calcium gluconate with viosterol was instituted with rapid subsidence of the carpopedal spasms. Ambulation was started on 7–16–46. The patient was discharged from the hospital on 7–31–46, having four to six liquid bowel movements daily.

The patient gained strength and returned to her home in Ohio in September 1946. A letter dated January 20, 1947, from the daughter who is a graduate nurse, states "The patient has been in the hospital three times since leaving Tucson. Her first visit was in October with the diagnosis of acute myocardial failure. Three weeks later with acute myocardial failure, pneumonia and pulmonary edema. Her third trip was last week for four days. I don't know what the last diagnosis was, but she coughed a lot and expectorated a lot of frothy bright red blood for the first two days. Between visits to the hospital she had been out of bed, knitting, etc. She weighs between 95 and 100 pounds.

FIG. 2.—Postoperative x-ray film, taken on July 30, 1946, showing length of small intestine remaining. The film is retouched for clarity. Due to rapid passage of barium it was necessary to superimpose another film to determine the exact outline before retouching.

Her appetite is excellent. She eats every four or five hours when awake. She has a partially formed stool each morning and about four hours after each meal, the latter stools are loose and frothy in appearance."

COMMENT

The term "massive" when applied to resection of the small bowel is indicative that the amount of intestine removed measures 200 cm. or more. The majority of reports on this subject which have appeared in the literature have

emphasized the amount of intestine removed. Little or no mention has been made as to the amount of bowel remaining to carry on the absorption and digestion for maintaining nutrition, yet this is the most important factor to be considered. This omission becomes more obvious when it is considered that the small bowel varies considerably between the races, the individual's diet, and the sexes. Bryant[3] found that the small intestine's length varied from 10 feet (304 cm.) to 28 feet 4 inches (863 cm.) in adults. It is shorter in women than in men and relatively longer in children. The Japanese and Russians, who eat coarse foods have longer intestines than races eating meats and more refined foods.

There are many reports of massive resection reported, beginning with Koeberle in 1880, with recovery of the patient (quoted from Haymond). Haymond made a thorough review of 257 cases of massive resection and found that the mortality was 33.5 per cent but concluded that this did not represent the true mortality because of the tendency to report only the successful cases. He concluded after studying these cases that a patient can withstand a resection of 33 per cent of the length of the small intestine with the expectation that the digestive tract will return to normal function; 50 per cent removal constitutes the upper limit of safety in extensive enterectomy and resection of more than 50 per cent must necessarily yield poorer results even though an exceptional case may do better than predicted. Sarnoff[4] states that the removal of 80 per cent proves fatal. In the case herein reported about 80 per cent of the small bowel was resected with survival.

The small intestine is the chief portion of the alimentary tract from which food stuffs are absorbed. No significant absorption occurs in the colon. The jejunum absorbs more fluid and sugars and the ileum absorbs the major portion of the digested proteins and fats. When a large segment of small bowel is removed compensation takes place in several ways. Flint[5] performed long enterectomies on dogs and found that the remaining portion did not grow in length but increased in diameter to twice the previous size. There was no regeneration in the crypts or villi, but an increase of 400 per cent in the absorbing surface was found. The villi are more numerous in the duodenum and jejunum, and in these regions the absorption rate is also the greatest. The surface area of the intestine, averaging one half square meter, is increased almost to 10 meters by means of these projections.[6] It is stated by Sarnoff that compensation for resection of the ileum is aided by an increase in gastric secretion, and gastric digestion lasts two hours longer. In our case 50 per cent of the barium was retained in the stomach after the remainder of the barium meal had advanced as far as the sigmoid. Wildegans[7] found that fats and proteins were not well digested during the first four weeks in dogs after resection of two-thirds of the intestine, but that the animals later regained this ability to a certain extent.

Metabolic studies were made by West et al[8, 9] of a man with all but three feet of small intestine resected. It was observed that carbohydrates were as well utilized as in normal individuals; 75 per cent of the protein and 55 per

cent of the fat were metabolized. The fecal fat consisted of 80 per cent fatty acids which indicated a good degree of digestion, but a considerable part of this may have occurred after the fat had reached the large intestine in which case it wouldn't have been absorbed. When a high fat diet was given, only 38 per cent of the fat was utilized and the patient developed a negative calcium balance manifested by tetany and a low blood calcium. The large amount of free fatty acids in the stool apparently carried the calcium away in the form of a calcium soap. It seems unlikely that these soaps would be absorbed except in the lower intestine since a significant degree of saponification would not occur in the usually acid contents of the duodenum and upper jejunum. Cosh[10] recorded a case of massive resection with achlorhydria who later developed tetany. He believed the anacidity was an important factor since the absorption of calcium which occurs primarily as calcium chloride in the upper intestinal tract is favored by an acid medium. West et al., noted a negative phosphorus balance in their patient; this could be accounted for on the basis of poor calcium absorption. On a high carbohydrate, low fat diet and a high calcium and vitamin D intake the phosphorus and calcium were brought into positive balance. In a case studied by Dragstedt, described by Haymond,[1] with only 55 cm. of small intestine functioning, it was found that a normal chloride balance was maintained. In our case a low blood cholesterol was present which was probably related to the inefficient lipid absorption. No reports have been found which compared the absorption and digestion within retained segments of ileum with those in which only jejunum remained intact. The greatest number of reports available for study neglected to state which portion of the small intestine remained after resection and this is an important factor in prognosis. A higher percentage of patients should show inanition if the upper segments (jejunum and/or duodenum) are removed than if the lower segments are resected. It is logical to assume that resection of the ileum is more often demanded than that of the upper small intestine. The lower bowel is much more liable to become involved in a volvulus (the most frequent reason for massive resection) and the same portion of intestine is more frequently affected by arterial emboli due to the fact that it receives its blood supply from the lower portion of the superior mesenteric artery where emboli are more likely to lodge. Other factors affecting prognosis are the length of the bowel remaining, its degree of compensatory reaction, the disease which necessitated its removal and the resistance of the patient.[11-12] Inadequate compensatory changes following massive resection of the small bowel result in a loss of weight, anemia, diarrhea, edema, tetany, weakness (potassium loss?) and possible vitamin deficiencies.

SUMMARY

A case of massive resection of the small intestine has been reviewed, in which no more than fourteen inches (35 cm.) of the jejunum was left remaining, with survival of the patient. She has manifested the same symptoms and findings as other such reported cases, namely poor fat digestion with frequent

fatty stools, associated low cholesterol and deficient calcium absorption. The carbohydrates and proteins were well metabolized. There was good response postoperatively on a high protein, high carbohydrate, low fat diet augmented by oral calcium and vitamin D.

BIBLIOGRAPHY

1 Haymond, H. E.: Massive Resection of the Small Intestine. Surg., Gynec. & Obst., **61**: 693, 1935.

2 Holman, C. C.: Survival After Removal of Twenty Feet of Intestine. Lancet, **19**: 597, 1944.

3 Bryant, J.: Observations on Growth and Length of the Human Intestine. Am. J. M. Sc., **167**: 499, 1924.

4 Sarnoff, J.: Extensive Resection of the Small Intestine. Ann. Surg., **78**: 745, 1923.

5 Flint, J. M.: Bull. Johns Hopkins Hosp., **23**: 127, 1912.

6 Wiggers, C. J.: Physiology in Health & Disease. Philadelphia, Lea & Febiger, 1944.

7 Wildegans, H.: Abstracted in J. A. M. A., **85**: 1, 436, 1925.

8 West, E. S., J. R. Montague and F. R. Judy: Digestion & Absorption in a Man with Three Feet of Small Intestine. Am. J. of Digest. Dis., **5**: 690, 1938.

9 Todd, W. R., M. Ditterbrandt, J. R. Montague and E. S. West: Digestion & Absorption in a Man with all but Three Feet of the Small Intestine Removed Surgically. Am. J. Digest. Dis., **7**: 295, 1940.

10 Cosh, J. A.: Tetany After Extensive Gut Resection. Lancet, **19**: pg. 596, 1944.

11 Prioleau, W. H.: Massive Resection of the Small Intestine. Ann. Surg., **119**: 372, 1944.

12 Greeley, P. W., and P. E. Greely: Extensive Resections of the Small Intestine. Illinois M. J., **67**: 45, 1935.

Thomas-Davis Clinic
130 S. Scott St.
Tucson, Arizona

BOOK REVIEW

Color Atlas of Hematology

By Roy D. Kracke, M.D., Dean of the Medical College of Alabama. 204 pages and 107 illustrations including 32 color plates. J. B. Lippincott Company, Philadelphia, $6.00.

This book was intended by the author to supply the need for a color atlas of hematology for the use of medical students, laboratory workers and general practitioners of medicine. The first 16 pages are occupied with definitions of hematological terms. Some of the definitions are needlessly restrictive: *Oxygen tension* is defined as applying to the bone marrow, photelometer as an instrument to measure the amount of hemoglobin. Others (like the Van den Bergh reaction) tell the purpose of the test without defining the reaction itself. This section is followed by a brief consideration of the origin and development of blood cells and a description of the morphology of the cells themselves accompanied by clear, well spaced out, colored drawings, paired with diagrams for the identification of each cell.

Other chapters deal with the hematologic appearance of various blood disorders (anemias, leukemias). Plate #17 illustrates the appearance of the blood in hemolytic jaundice but fails to delineate the presence of spherocytes, though they are alluded to in the explanatory text. Döhle bodies, not uncommonly seen in septicemias, are not mentioned anywhere, though one polymorphonuclear leukocyte containing them may be found in plate #14. Auer bodies are not mentioned or illustrated. The later chapters of this useful manual deal with the technic of various hematological determinations, an illustrated discussion of common blood parasites, and the appearance of the blood cells of certain common laboratory animals. The book fulfills rather well its chief purpose, namely, to supply pictorial and descriptive information for the guidance of workers in this field.

Leandro M. Tocantins.

BOOKS RECEIVED

1. Samuels, Jules: Die Hornonalen Aspekte des Fortpflanzgsprozesses. Holdert & Company, N. V., Amsterdam, Holland, 1946.
2. Samuels, Jules: Die Hormonversorgung des Foetus. E. J. Brill, Leiden, 1947.
3. Gordon, Edgar S.: Nutritional and Vitamin Therapy in General Practice. The Year Book Publishers, Inc., Chicago, Illinois, 1940.
4. Goldberg, Morris: English-Spanish Chemical and Medical Dictionary. McGraw-Hill Book Company, Inc., New York, 1947.
5. Woerdeman, M. W. *et al*, Editors: Excerpta Medica: Radiology, Section XIV, Vol. I, No. 1 N. V. Excerpta Medica, Kalverstraat, Amsterdam C., June, 1947.
6. Elman, Robert: Parental Alimentation in Surgery. Paul B. Hoeber, Inc., New York, 1945.
7. Milch, Henry: Osteotomy of the Long Bones. Charles C. Thomas, Springfield, Illinois, 1947.
8. Kessler, Henry H.: Cineplasty. Charles C. Thomas, Springfield, Illinois, 1947.
9. Demel, Rudolf: Chirurgie der Inflektionen. Verlag Wilhelm Maudrich, Wein, 1947.
10. Samuels, Jules: Endogeneous Endocrinotherapy, including the Causal Cure of Cancer; Compendium. Holdert & Company, Amsterdam, 1947.
11. May, Hans: Reconstructive and Reparative Surgery. F. A. Davis Company, Philadelphia, 1947.

12. TURNER, C. GIL:	El Enclavamiento Intramedular de Kuntscher. Revista Espanola de Cirugia, Madrid, 1946.
13. DONALDSON, J. K.:	Surgical Disorders of the Chest: Diagnosis and Treatment. Lea and Febiger, Philadelphia, 1947.
14. CRILE, GRACE, Editor:	George Crile: An Autobiography. J. B. Lippincott Company, Philadelphia, 1947.
15. FERGUSON, L. KRAEER:	Surgery of the Ambulatory Patient. J. B. Lippincott Company, Philadelphia, 1947.
16. SAUL, LEON J.:	Emotional Maturity: The Development and Dynamics of Personality. J. B. Lippincott Company, Philadelphia, 1947.
17. ROSEN, GEORGE AND CASPARI-ROSEN BEATE	400 Years of a Doctor's Life. Henry Schuman, New York, 1947.

EDITORIAL ADDRESS

Original typed manuscripts and illustrations submitted to this Journal should be forwarded prepaid, at the author's risk, to the Chairman of the Editorial Board of the ANNALS OF SURGERY.

John H. Gibbon, Jr., M.D.
1025 Walnut Street, Philadelphia 7, Pa.

Contributions in a foreign language when accepted will be translated and published in English.

Exchanges and Books for Review should be sent to Dr. Gibbon at the above address.

Subscriptions, advertising and all business communications should be addressed

ANNALS OF SURGERY
East Washington Square, Philadelphia, Pa.